TITLE OF THE INVENTION

PPAR ALPHA SELECTIVE COMPOUNDS FOR THE TREATMENT OF DYSLIPIDEMIA AND OTHER LIPID DISORDERS

FIELD OF THE INVENTION

The instant invention is concerned with a class of benzodihydrofuran compounds and pharmaceutically acceptable salts thereof which are useful as therapeutic compounds, particularly in the treatment and control of hyperlipidemia, hypercholesterolemia, dyslipidemia, and other lipid disorders, and in delaying the onset of or reducing the risk of conditions and sequelae that are associated with these diseases, including atherosclerosis and Type 2 diabetes mellitus, often referred to as non-insulin dependent diabetes (NIDDM).

BACKGROUND OF THE INVENTION

Disorders of lipid metabolism (dyslipidemias) include various conditions characterized by abnormal concentrations of one or more lipids (i.e. cholesterol and triglycerides), and/or apolipoproteins (i.e., apolipoproteins A, B, C and E), and/or lipoproteins (i.e., the macromolecular complexes formed by the lipid and the apolipoprotein that allow lipids to circulate in blood, such as Low Density Lipoproteins (LDL), Very Low Density Lipoproteins (VLDL) and Intermediate Density Lipoproteins (IDL)). Cholesterol is mostly carried in Low Density Lipoproteins (LDL), and this component is commonly known as the "bad" cholesterol because it has been shown that elevations in LDL-cholesterol correlate closely to the risk of coronary heart disease. A smaller component of cholesterol is carried in the High Density Lipoproteins (HDL) and is commonly known as the "good" cholesterol. In fact, it is known that the primary function of HDL is to accept cholesterol deposited in the arterial wall and to transport it back to the liver for disposal through the intestine. Although it is desirable to lower elevated levels of LDL cholesterol, it is also desirable to increase levels of HDL cholesterol. Generally, it has been found that increased levels of HDL are associated with a lower risk for coronary heart disease (CHD). See, for example, Gordon, et al., Am. J. Med., *62*, 707-714 (1977); Stampfer, et al., N. England J. Med., *325*, 373-381 (1991); and Kannel, et al., Ann. Internal Med., *90*, 85-91 (1979). An example of an HDL raising agent is nicotinic acid, a drug with limited utility because doses that achieve HDL raising are associated with undesirable effects, such as flushing.

Dyslipidemias were originally classified by Fredrickson according to the combination of alterations mentioned above. The Fredrickson classification includes 6 phenotypes (i.e., I, IIa, IIb, III, IV and V) with the most common being the isolated hypercholesterolemia (or type IIa) which is usually accompained by elevated concentrations of total and LDL cholesterol. The initial treatment for hypercholesterolemia is often to modify the diet to one low in fat and cholesterol, coupled with appropriate physical exercise, followed by drug therapy when LDL-lowering goals are not met by diet and exercise alone

A second common form of dyslipidemia is the mixed or combined hyperlipidemia or type IIb and III of the Fredrickson classification. This dyslipidemia is often prevalent in patients with type 2 diabetes, obesity and the metabolic syndrome. In this dyslipidemia there are modest elevations of LDL-cholesterol, accompanied by more pronounced elevations of small dense LDL-cholesterol particles, VLDL and/or IDL (i.e., triglyceride rich lipoproteins), and total triglycerides. In addition, concentrations of HDL are often low.

Peroxisome proliferators are a structurally diverse group of compounds that when administered to rodents elicit dramatic increases in the size and number of hepatic and renal peroxisomes, as well as concomitant increases in the capacity of peroxisomes to metabolize fatty acids via increased expression of the enzymes of the beta-oxidation cycle. Compounds of this group include but are not limited to the fibrate class of lipid modulating drugs, herbicides, phthalate plasticizers and the glitazones, a class of compounds that has been under investigation for the treatment of type 2 diabetes. Peroxisome proliferation is also triggered by dietary or physiological factors such as a high-fat diet and cold acclimatization.

Three sub-types of peroxisome proliferator activated receptor (PPAR) have been discovered and described; they are peroxisome proliferator activated receptor alpha (PPARα), peroxisome proliferator activated receptor gamma (PPARγ) and peroxisome proliferator activated receptor delta (PPARδ). PPARα is activated by a number of medium and long-chain fatty acids, and it is involved in stimulating β–oxidation of fatty acids. PPARα is also associated with the activity of fibrates and fatty acids in rodents and humans. Fibric acid derivatives such as clofibrate, fenofibrate, bezafibrate, ciprofibrate, beclofibrate and etofibrate, as well as gemfibrozil, each of which are PPARα ligands and/or activators, produce a substantial reduction in plasma triglycerides as well as some increase in HDL. The effects on LDL cholesterol are inconsistent and might depend upon the compound and/or the

dyslipidemic phenotype. For these reasons, this class of compounds has been primarily used to treat hypertriglyceridemia (i.e, Fredrickson Type IV and V) and/or mixed hyperlipidemia.

The PPARγ receptor subtypes are involved in activating the program of adipocyte differentiation and are not involved in stimulating peroxisome proliferation in the liver. There are two known protein isoforms of PPARγ : PPARγ1 and PPARγ2 which differ only in that PPARγ2 contains an additional 28 amino acids present at the amino terminus. The DNA sequences for the human isotypes are described in Elbrecht, et al., BBRC *224*;431-437 (1996). In mice, PPARγ2 is expressed specifically in fat cells. Tontonoz *et al., Cell 79*: 1147-1156 (1994) provide evidence to show that one physiological role of PPARγ2 is to induce adipocyte differentiation. As with other members of the nuclear hormone receptor superfamily, PPARγ2 regulates the expression of genes through interaction with other proteins and binding to hormone response elements, for example in the 5' flanking regions of responsive genes. An example of a PPARγ2 responsive gene is the tissue-specific adipocyte P2 gene. Although peroxisome proliferators, including the fibrates and fatty acids, activate the transcriptional activity of PPAR's, only prostaglandin J_2 derivatives have been identified as potential natural ligands of the PPARγ subtype, which also binds thiazolidinedione antidiabetic agents with high affinity.

The human nuclear receptor gene PPARδ (hPPARδ) has been cloned from a human osteosarcoma cell cDNA library and is fully described in A. Schmidt et al., *Molecular Endocrinology*, *6* :1634-1641 (1992). It should be noted that PPARδ is also referred to in the literature as PPARβ and as NUC1, and each of these names refers to the same receptor; in Schmidt *et al.* the receptor is referred to as NUC1.

In WO96/01430, a human PPAR subtype, hNUC1B, is disclosed. The amino acid sequence of hNUC1B differs from human PPARδ (referred to therein as hNUC1) by one amino acid, i.e., alanine at position 292. Based on in vivo experiments described therein, the authors suggest that hNUC1B protein represses hPPARα and thyroid hormone receptor protein activity.

It has been disclosed in WO97/28149 that agonists of PPARδ are useful in raising HDL plasma levels. PPARδ agonists have recently been disclosed in US Provisional Application Serial No. 60/297,356 as having utility in the treatment of various inflammatory diseases, such as rheumatoid arthritis. WO97/27857, 97/28115, 97/28137 and 97/27847 disclose compounds that are useful as antidiabetic,

antiobesity, anti-atherosclerosis and antihyperlipidemic agents, and which activate PPARs.

It is generally believed that glitazones exert their effects by binding to the peroxisome proliferator activated receptor (PPAR) family of receptors, controlling certain transcription elements having to do with the biological entities listed above. Glitazones are benzyl-2,4-thiazolidinedione derivatives. See Hulin et al., Current Pharm. Design (1996) 2, 85-102.

A number of glitazones that are PPAR agonists have been approved for use in the treatment of diabetes. These include troglitazone, rosiglitazone and pioglitazone, all of which are primarily or exclusively PPARγ agonists. Many of the newer PPAR agonists that are currently under development or are in clinical trials have dual PPARα and γ activity, such as KRP-297. The PPARα/γ agonists are expected to improve both insulin sensitivity and the lipid profile in patients having NIDDM.

Although glitazones have been beneficial in the treatment of NIDDM, there have been some serious adverse events associated with the use of the compounds, especially troglitazone, which was eventually withdrawn. The most serious adverse events have been liver toxicity, which resulted in a number of deaths. Because of the problems that have occurred with the glitazones, researchers in a number of laboratories have been investigating classes of PPAR agonists that do not contain 1,3-thiazolidinedione moieties and therefore are not glitazones.

Compounds that are agonists of the various PPAR sub-types are expected to be useful in the treatment of diseases and conditions that respond to treatment with PPAR agonists, regardless of whether the compounds are glitazones. These include dyslipidemia, diabetes, and related conditions. PPARα agonists improve the lipid profile and alleviate dyslipidemias by reducing elevated LDL levels, reducing elevated triglyceride levels, and increasing HDL levels. PPARγ agonists improve insulin sensitivity, reducing the need for insulin secretagogues and insulin injections in patients with NIDDM. The role of PPARδ is less well defined, but PPARδ also appears to help control hyperlipidemia and hyperglycemia in type 2 diabetic patients.

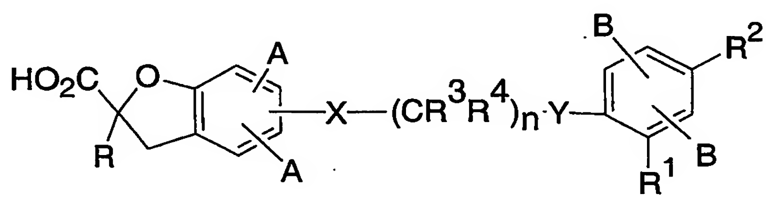
SUMMARY OF THE INVENTION

The class of compounds described herein is a new class of potent and selective PPARα agonists that do not contain a 1,3-thiazolidinedione moiety. The

compounds generally exhibit high activity at the PPARα receptor and little or no activity at the PPARγ and PPARδ receptors, as evidenced by their assay data. The compounds are useful in the treatment of diseases, disorders and conditions that are treated or ameliorated by PPARα agonists.

The compounds are useful in treating one or more of the following conditions: mixed or diabetic dyslipidemia; other lipid disorders, including isolated hypercholesterolemia as manifested by elevations in LDL-C and/or non-HDL-C; hyperapoBliproteinemia; hypertriglyceridemia; elevated triglyceride-rich-lipoproteins; and low HDL cholesterol concentrations. The compounds may also have utility in the treatment of atherosclerosis, obesity, and vascular restenosis. They may also potentially be useful in treating inflammatory conditions and insulin sensitivity. As a result of their utility in treating and ameliorating one or more of lipid disorders, obesity, dyslipidemia, and insulin sensitivity, the compounds also may be effective in treating or ameliorating the metabolic syndrome, also known as Syndrome X. They may also help to reduce the risk of developing atherosclerosis.

The present invention provides compounds having the structure of Formula I, including pharmaceutically acceptable salts and prodrugs of these compounds:



I

In the compounds of Formula I,

R is selected from a group of substituents consisting of

(a) C_1-C_6 alkyl, which is optionally substituted with 1-5 halogens independently selected from F and Cl, and
(b) -$(CH_2)_{0-2}C_3$-C_6 cycloalkyl, wherein said cycloalkyl is optionally substituted with 1-2 groups independently selected from halogen, CH_3, and CF_3;

R^1 is selected from a group of substituents consisting of

(a) Cl,
(b) F,
(c) C_1-C_4alkyl, which is optionally substituted with 1-5 halogens independently selected from F and Cl, and
(d) -$(CH_2)_{0-2}C_3$-C_6 cycloalkyl, wherein said cycloalkyl is optionally substituted with 1-3 groups independently selected from halogen, CH_3, and CF_3;

R^2 is selected from a group of substituents consisting of

(a) -OC_1-C_6alkyl, which is optionally substituted with 1-5 halogens independently selected from F and Cl,
(b) -SC_1-C_6alkyl, which is optionally substituted with 1-5 halogens independently selected from F and Cl,
(c) $(CH_2)_{0-3}C_3$-C_6cycloalkyl, wherein said cycloalkyl is optionally substituted with 1-3 groups independently selected from halogen, CH_3, and CF_3; and
(d) C_1-C_6alkyl, which is optionally substituted with 1-5 halogens independently selected from F and Cl;

Each R^3 and each R^4 is independently selected from H, Cl, F, and C_1-C_3alkyl, wherein C_1-C_3alkyl is optionally substituted with 1-3 halogens, which are independently selected from Cl and F;

The substituents A and the substituents B may be alike or different. Each A and each B is independently selected from the group consisting of

(a) H,
(b) Halogen,
(c) C_1-C_6alkyl, which is optionally substituted with 1-5 halogens independently selected from F and Cl, and
(d) -O C_1-C_6alkyl, which is optionally substituted with 1-5 halogens independently selected from F and Cl;

X and Y are independently selected from O, S, and CR^3R^4; and

n is an integer from 1-3.

In the above summary, reference to alkyl groups by carbon number, such as C_3 alkyl or C_{3-6} alkyl, refers to both linear and branched alkyl groups.

The compounds described above are effective in treating diseases or conditions that respond to treatment with PPARα agonists. The compounds are expected to be efficacious in treating and ameliorating one or more of the following diseases or conditions: hyperlipidemia, dyslipidemia, hypercholesterolemia, hypertrigyceridemia, hyperglycemia, and obesity. The compounds may also be efficacious in treating non-insulin dependent diabetes mellitus (NIDDM) and/or conditions that are often associated with NIDDM, but which may be present in non-diabetic patients as well, including hyperlipidemia, dyslipidemia, hypercholesterolemia, hypertrigyceridemia, and obesity. The compounds may also be effective in treating atherosclerosis, hyperinsulinemia, vascular restenosis, and inflammatory conditions. The compounds may be effective in delaying or reducing the risk of some of the sequelae of NIDDM, such as atherosclerosis, vascular restenosis, and retinopathy by ameliorating the conditions that contribute to the development of these diseases. They may also be effective in reducing cardiovascular events that occur in human patients having metabolic syndrome, such as coronary heart disease, by ameliorating some of the risk factors that are associated with metabolic syndrome.

DETAILED DESCRIPTION OF THE INVENTION

The invention has numerous embodiments. Several preferred sub-groups of compounds are described below:

One embodiment of the invention comprises compounds of formula I in which X and Y are each independently selected from S and O.

Another embodiment comprises compounds of Formula I, wherein X and Y are O.

In another embodiment, each R^3 and each R^4 is independently selected from H, Cl, F, CH_3, and CF_3.

In some preferred embodiments, R^3 and R^4 of Formula I are H.

In other embodiments, R is C_1-C_4 alkyl, which optionally may be substituted with 1-3 F.

In additional subsets of compounds of Formula I, each A and each B is independently selected from H, Cl, F, Br, CH_3, CF_3, $-OCH_3$, and $-OCF_3$.

In other preferred subsets of compounds of Formula I, A and B are both H.

Another subset of compounds of Formula I comprises compounds where R^1 is selected from Cl and C_2-C_4alkyl, where C_2-C_4alkyl is optionally substituted with 1-5 halogens independently selected from F and Cl.

An additional embodiment comprises compounds of Formula I in which R^1 is selected from Cl and C_2-C_4 alkyl.

Another embodiment of the invention comprises compounds of Formula I in which R^2 is selected from C_1-C_5alkyl, $-OC_1$-C_5alkyl, and $-SC_1$-C_5alkyl, where C_1-C_5alkyl, $-OC_1$-C_5alkyl, and $-SC_1$-C_5alkyl optionally are substituted with 1-5 F atoms.

In many preferred compounds of Formula I, n is 2 or 3.

A preferred group of compounds of Formula I, including pharmaceutically acceptable salts thereof, is described as follows:

R is C_1-C_4 alkyl, which is optionally substituted with 1-3 F;

R^1 is selected from Cl and C_2-C_4alkyl;

R^2 is selected from C_1-C_5alkyl, -OC_1-C_5alkyl, and -SC_1-C_5alkyl, where C_1-C_5alkyl, -OC_1-C_5alkyl, and -SC_1-C_5alkyl are optionally substituted with 1-5 F;

R^3, R^4, A, and B are H;

X and Y are O; and

n is 2 or 3.

Specific examples of compounds of this invention are provided as Examples 1-24, listed by name below. Their structures are summarized in the Table immediately before the Examples. The following compounds, including pharmaceutically acceptable salts and prodrugs of these compounds, are specific embodiments of this invention:

Example 1: 5-{3-[2-Chloro-4-(2,2,2-trifluoro-ethoxy)-phenoxy]-propoxy}-2-methyl-2,3-dihydro-benzofuran-2-carboxylic acid.

Example 2: 5-{3-[4-(2,2-Dimethyl-propyl)-2-propyl-phenoxy]-propoxy}-2-methyl-2,3-dihydro-benzofuran-2-carboxylic acid.

Example 3: 5-[3-(2-Chloro-4-trifluoromethoxy-phenoxy)-propoxy]-2-methyl-2,3-dihydro-benzofuran-2-carboxylic acid.

Example 4: 5-{3-[4-(2,2-Dimethyl-propyl)-2-propyl-phenoxy]-propoxy}-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid.

Example 5: 2-Ethyl-5-[3-(2-propyl-4-trifluoromethylsulfanyl-phenoxy)-propoxy]-2,3-dihydro-benzofuran-2-carboxylic acid.

Example 6: 5-[3-(2-Chloro-4-trifluoromethylsulfanyl-phenoxy)-propoxy]-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid.

Example 7: 5-[3-(4-*tert*-Butyl-2-chloro-phenoxy)-propoxy]-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid.

Example 8: 5-[3-(2-Chloro-4-trifluoromethyl-phenoxy)-propoxy]-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid.

Example 9: 5-{3-[2-Chloro-4-(1,1-dimethyl-propyl)-phenoxy]-propoxy}-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid.

Example 10: (2*S*)-5-[3-(2-Chloro-4-trifluoromethoxy-phenoxy)-propoxy]-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid.

Example 11: (2*S*)-5-{3-[2-Chloro-4-(2,2-dimethyl-propyl)-phenoxy]-propoxy}-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid.

Example 12: (2*S*)-5-{3-[2-Chloro-4-(2,2,2-trifluoro-ethoxy)-phenoxy]-propoxy}-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid.

Example 13: (2*S*)-5-{3-[2-Chloro-4-(3,3,3-trifluoro-propyl)-phenoxy]-propoxy}-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid.

Example 14: (2*S*)-5-{3-[2-Chloro-4-(2,2,2-trifluoro-ethyl)-phenoxy]-propoxy}-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid.

Example 15: 6-[3-(2-Chloro-4-trifluoromethoxy-phenoxy)-propoxy]-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid.

Example 16: (2*S*)- 5-[4-(2-Chloro-4-trifluoromethoxy-phenyl)-butoxy]-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid.

Example 17: (2*R*)-5-{3-[2-Chloro-4-(2,2-dimethyl-propyl)-phenoxy]-propoxy}-2-isopropyl-2,3-dihydro-benzofuran-2-carboxylic acid.

Example 18: (2*R*)-5-[3-(2-Chloro-4-trifluoromethoxy-phenoxy)-propoxy]-2-isopropyl-2,3-dihydro-benzofuran-2-carboxylic acid.

Example 19: (2*R*)-5-{3-[2-Chloro-4-(2,2,2-trifluoro-ethyl)-phenoxy]-propoxy}-2-isopropyl-2,3-dihydro-benzofuran-2-carboxylic acid.

Example 20: (2*R*)-5-[4-(2-Chloro-4-trifluoromethoxy-phenoxy)-butyl]-2-isopropyl-2,3-dihydro-benzofuran-2-carboxylic acid.

Example 21: (2*R*)- 2-*tert*-Butyl-5-{3-[2-chloro-4-(2,2,2-trifluoro-ethyl)-phenoxy]-propoxy}-2,3-dihydro-benzofuran-2-carboxylic acid.

Example 22: 5-{3-[2-Chloro-4-(2,2,2-trifluoro-ethyl)-phenoxy]-propoxy}-2-trifluoromethyl-2,3-dihydro-benzofuran-2-carboxylic acid.

Example 23: (2*R*)-5-[2-(2-Chloro-4-trifluoromethoxy-phenoxy)-ethoxy]-2-isopropyl-2,3-dihydro-benzofuran-2-carboxylic acid.

Example 24: (2*R*)- 2-*tert*-Butyl-5-[2-(2-chloro-4-trifluoromethoxy-phenoxy)-ethoxy]-2,3-dihydro-benzofuran-2-carboxylic acid.

The invention further includes pharmaceutical compositions comprising any of the compounds described above and a pharmaceutically acceptable carrier.

The invention further includes pharmaceutical compositions comprising any of the compounds described herein, including pharmaceutically acceptable salts, and a pharmaceutically acceptable carrier.

Definitions

"Alkyl", as well as other groups having the prefix "alk", such as alkoxy or alkenyl, means carbon chains which may be linear or branched, including chains with multiple branch points, unless the carbon chain is defined otherwise. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, and the like. Isopropyl and sec- and tert-butyl are branched.

"Alkenyl" means carbon chains which contain at least one carbon-carbon double bond, and which may be linear or branched. Examples of alkenyl include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, and the like.

"Cycloalkyl" means a mono- or bicyclic saturated carbocyclic ring having from 3 to 10 carbon atoms, unless otherwise stated. The term also includes a monocyclic or bicyclic saturated carbocyclic ring which is fused to another cyclic group, such as an aryl group. Examples of cycloalkyl include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like.

"Aryl" (and "arylene") when used to describe a substituent or group in a structure means a monocyclic or bicyclic or tricyclic group or substituent in which all of the rings are aromatic and which contains only carbon ring atoms. "Aryl" groups can be fused to other cyclic groups, such as a cycloalkyl or heterocyclic group. Examples of aryl substituents include phenyl and naphthyl. Phenyl is the preferred aryl group.

"Heterocycle" means a fully or partially saturated ring containing at least one heteroatom selected from N, S and O, where the ring has from 3 to 10 atoms, unless otherwise defined.

"Heteroaryl" (and "heteroarylene") means an aromatic ring containing at least one ring heteroatom selected from N, O and S (including SO and SO_2), where the ring contains 5-6 atoms. Examples of heteroaryl include pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridyl, oxazolyl, oxadiazolyl, thiadiazolyl, thiazolyl,

imidazolyl, triazolyl, tetrazolyl, furanyl, triazinyl, thienyl, pyrimidyl, pyridazinyl, and pyrazinyl. Heteroaryl and aromatic rings can be fused together to form bicyclic or tricyclic ring systems, as for example benzisoxazolyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, benzothiophenyl (including S-oxide and dioxide), quinolyl, indolyl, isoquinolyl, dibenzofuran and the like.

"Halogen" includes fluorine, chlorine, bromine and iodine. Fluorine is generally the most preferred halogen substituent on an alkyl group.

"Me" and "Et" represent methyl and ethyl respectively.

The term "administration of" or "administering" a compound means providing a compound of this invention or a prodrug of a compound of this invention to a patient in need of treatment.

To treat, as a disease or condition, means to deal with the disease or condition in a specified manner.

Amelioration of a disease or condition means improving the disease or condition or making it better.

"Metabolic Syndrome" is defined in the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol In Adults (ATP-III). E.S. Ford et al., JAMA, vol. 287 (3), Jan. 16, 2002, pp 356-359. Briefly, a person is defined as having metabolic syndrome if the person has three or more of the the following symptoms: abdominal obesity, hypertriglyceridemia, low HDL cholesterol, high blood pressure, and high fasting plasma glucose. The criteria for these are defined in ATP-III.

The "patient" to whom the compounds of this invention can be administered may be selected from mammals, including primates, such as monkeys and apes; bovines, such as cows; equines, such as horses; canines, such as dogs; felines, such as cats; ovines, such as goats and sheep; and rodents, such as mice, rats, and guinea pigs. Patients may also include non-mammalian species, such as chickens and other birds. The preferred patient is a human.

The term "composition," as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition

made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

Optical Isomers - Diastereomers - Geometric Isomers - Tautomers

Compounds of Formula I may contain one or more asymmetric centers. The compounds can thus occur as racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The present invention is meant to comprehend all such isomeric forms of the compounds of Formula I.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Some of the compounds described herein may exist with different points of attachment of hydrogen coupled with double bond shifts, referred to as tautomers. An example is a carbonyl (e.g. a ketone) and its enol form, often known as keto-enol tautomers. The individual tautomers as well as mixtures thereof are encompassed with compounds of Formula I.

If desired, racemic mixtures of compounds of Formula I may be separated by means of classical resolution through fractional crystallization of salts formed with enantiomerically pure acids or bases. Other diasteromeric derivatives can be formed by the coupling of a racemic mixture of the compounds of Formula I to an enantiomerically pure compound. Such diastereomeric mixture may be separated by standard chromatographic methods or recrystallization protocols. These diasteromeric derivatives may then be converted to the pure enantiomers of the compounds of Formula I by cleavage of the added chiral residue. The racemic mixture of the compounds of Formula I can also be separated directly by chromatographic methods utilizing chiral stationary phases, of which many examples are known in the literature.

Alternatively, any enantiomer of a compound of the general Formula I may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration.

Compounds of Formula I that have more than one asymmetric center and that occur as diasteromeric mixtures can similarly be separated into individual diastereomers by standard methods, and these can be separated to individual enantiomers as described above.

Salts

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. For the carboxylic acid compounds of Formula I, salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganous, manganic, potassium, sodium, and zinc salts and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts in the solid form may exist in more than one crystal structure, and may also be in the form of hydrates. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

For compounds that are basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

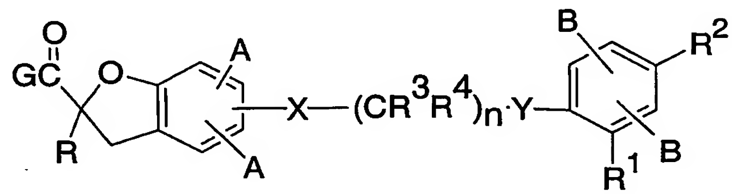
It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

Metabolites – Prodrugs

Prodrugs are compounds that are converted to the claimed compounds as they are being administered to a patient or after they have been administered to a patient. The prodrugs are compounds of this invention, and the active metabolites of the prodrugs, where the metabolites have Formula I, are also compounds of the invention. A non-limiting example of a prodrug of the carboxylic acids of this

invention is an ester of the carboxylic acid, as for example a C_1 to C_6 ester, or an ester which has functionality that makes it more easily hydrolyzed after administration to a patient.

Examples of prodrugs of this class of compounds may be described as compounds having Formula Ia, where G is a group that is easily removed under



Ia

physiological conditions during or after administration to a mammalian patient to yield the free carboxylic acid or carboxylate salt thereof, where G has been converted to OH, or the carboxylate salt thereof. The other substituents in Formula Ia are as previously defined for Formula I.

Examples of prodrugs of Formula Ia include compounds in which G is selected from the group consisting of $-OR^a$, $-OCH_2OR^a$, $-OCH(CH_3)OR^a$, $-OCH_2OC(O)R^a$, $-OCH(CH_3)OC(O)R^a$, $-OCH_2OC(O)OR^a$, $-OCH(CH_3)OC(O)OR^a$, and $-NR^bR^b$, where each R^a is independently selected from C_{1-6} alkyl which is optionally substituted with one or two groups selected from $-CO_2H$, $-CONH_2$, $-NH_2$, -OH, -OAc, -NHAc, and phenyl; and wherein each R^b is independently selected from H and R^a.

Utilities

Compounds of the present invention are potent agonists of the peroxisome proliferator activated receptor subtypes, particularly PPARα, with little or no activity with respect to PPARγ or PPARδ. Compounds of the present invention are thus selective and potent agonists of the subtype PPARα. Compounds of the present invention are useful in treating, controlling or ameliorating diseases, disorders and conditions, where the treatment, control or amelioration is effected by the activation of the PPARα subtype.

An important aspect of this invention is that it provides a method for the treatment, control, or amelioration of various lipid disorders, including

dyslipidemia, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, low HDL levels, high LDL levels, and atherosclerosis and its sequelae, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound having formula I.

The compounds as defined herein may be used in treating or controlling or ameliorating one or more of the following diseases or conditions in a mammalian or human patient in need of treatment, where the treatment comprises the administration of a therapeutically effective amount of a compound of Formula I to the patient in need of treatment:

(1) lipid disorders;
(2) hyperlipidemia;
(3) low HDL-cholesterol;
(4) high LDL-cholesterol;
(5) hypercholesterolemia;
(6) hypertriglyceridemia;
(7) dyslipidemia, including high LDL cholesterol and low HDL cholesterol; and
(8) atherosclerosis, including sequelae of atherosclerosis (angina, claudication, heart attack, stroke, etc.).

More generally, compounds having Formula I may be used to treat or control or ameliorate one or more of the following diseases, disorders and conditions, by the administration of a therapeutically effective amount of a compound of Formula I: (1) lipid disorders, (2) dyslipidemia, (3) hyperlipidemia, (4) hypertriglyceridemia, (5) hypercholesterolemia, (6) low HDL levels, (7) high LDL levels, (8) atherosclerosis and its sequelae, (9) obesity, including abdominal obesity (10) vascular restenosis, (11) retinopathy, (12) non-insulin dependent diabetes mellitus (NIDDM), (13) hyperglycemia, (14) impaired glucose tolerance, (15) insulin resistance, (16) irritable bowel syndrome, (17) inflammatory bowel disease, including Crohn's disease and ulcerative colitis, (18) pancreatitis, (19) other inflammatory conditions, (20) neurodegenerative disease, (21) Alzheimer's disease, (22) psoriasis, (23) acne vulgaris, (24) other skin diseases and dermatological conditions modulated by PPAR, (25) high blood pressure, (26) cachexia, and (27) the metabolic syndrome, sometimes known as Syndrome X.

The compounds may also be useful in the treatment of (1) neoplastic conditions, (2) adipose cell tumors, (3) adipose cell carcinomas, such as

liposarcoma, (4) prostate cancer and other cancers, including gastric, breast, bladder and colon cancers, and (5) angiogenesis.

Other conditions which may be treated with the compounds of this invention include ovarian hyperandrogenism (polycystic ovarian syndrome), cachexia, and other disorders where insulin resistance is a component.

The present invention is further directed to a method for the manufacture of a medicament that is useful for the treatment of a disease or condition that is treated by the administration of a PPARα agonist, wherein the method comprises combining an effective amount of the compound of Formula I with a pharmaceutically acceptable carrier or diluent.

Another aspect of the invention provides a method of treating cachexia. PPARα is known to be necessary for an appropriate energy sparing response to starvation, and inappropriate metabolism and energy utilization is clearly responsible for the wasting of cachexia. The compounds of this invention may therefore be useful in the treatment of cachexia.

In another aspect, the invention provides a method of treating inflammatory conditions, including inflammatory bowel disease, Crohn's disease, and ulcerative colitis, by administration of an effective amount of a PPARα agonist of Formula I. Additional inflammatory diseases that may be treated with the instant invention include gout, rheumatoid arthritis, osteoarthritis, multiple sclerosis, asthma, ARDS, psoriasis, vasculitis, ischemia/reperfusion injury, and related diseases.

Another aspect of the invention provides a method of treating a variety of skin diseases and dermatological conditions that are modulated by PPARα agonists by administering an effective amount of a compound of Formula I to a mammalian or human patient in need of such treatment. These diseases and conditions include psoriasis and acne vulgaris. Examples of other skin diseases and dermatological disorders that may be treated include eczema; lupus associated skin lesions; dermatitides such as seborrheic dermatitis and solar dermatitis; keratoses such as seborrheic keratosis, senile keratosis, actinic keratosis, photo-induced keratosis, and keratosis follicularis; keloids and prophylaxis against keloid formation, warts including verruca, condyloma, or condyloma accuminatum, and human papilloma viral (HPV) infections such as venereal warts, viral warts, molluscum contagiosum, leukoplakia, lichen planus, keratitis, skin cancer such as basal cell carcinoma, cutaneous T cell lymphoma and localized benign epidermal tumors (keratoderma, epidermal naevi).

Administration and Dose Ranges .

Any suitable route of administration may be employed for providing a mammal, especially a human, with an effective dose of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like. Preferably compounds of Formula I are administered orally.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated. Such dosage may be ascertained readily by a person skilled in the art.

When treating hypertriglyceridemia, hypercholesterolemia, dyslipidemia, hyperlipidemia, and other diseases for which compounds of Formula I are indicated, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.1 milligram to about 100 milligram per kilogram of animal body weight, preferably given as a single daily dose or in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 1.0 milligrams to about 1000 milligrams, preferably from about 1 milligrams to about 50 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 1 milligram to about 350 milligrams. This dosage regimen will vary depending on the specific compound and also the patient. The dosage may be adjusted within the ranges recited above or even outside those ranges in order to provide the optimal therapeutic response.

Pharmaceutical Compositions

Another aspect of the present invention provides pharmaceutical compositions which comprise a compound of Formula I and a pharmaceutically acceptable carrier. The pharmaceutical compositions of the present invention comprise a compound of Formula I or a pharmaceutically acceptable salt or prodrug thereof as an active ingredient, as well as a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. More typically, a selected compound of Formula I, or a pharmaceutically acceptable salt thereof, will be the only active ingredient in a composition. The term "pharmaceutically acceptable salts" refers to

salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic bases or acids and organic bases or acids.

The compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

In practical use, the compounds of Formula I can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, hard and soft capsules and tablets, with the solid oral preparations being preferred over the liquid preparations.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. The active compounds can also be administered intranasally as, for example, liquid drops or spray.

The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a

lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Compounds of formula I may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

Combination Therapy

The compounds of this invention may be used in combination with other drugs that may also have utility in the treatment of the diseases or conditions for which compounds of Formula I are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of Formula I. When a compound of Formula I is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and the compound of Formula I is preferred. However, the combination therapy also includes therapies in which the compound of Formula I and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in combination with

one or more other active ingredients, the compound of the present invention and the other active ingredients may be used in lower doses than when each is used singly. Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to a compound of Formula I.

For example, the compounds of Formula I may be administered in combination with one or more other lipid lowering drugs, including (1) a cholesterol biosynthesis inhibitor, including but not limited to, an HMG-CoA reductase inhibitor, such as lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, itavastatin, rosuvastatin, and ZD-4522; (2) a cholesterol absorption inhibitor (for example a stanol ester, a sterol glycoside such as tiqueside, or an azetidinone such as ezetimibe); (3) an ACAT inhibitor (such as avasimibe), (4) niacin; (5) a bile acid sequestrant; (6) a microsomal triglyceride transport inhibitor; (7) a bile acid reuptake inhibitor; and (8) a PPARα/γ agonist, such as KRP-297. These combination treatments are expected to be particularly effective for the treatment or control of one or more lipid disorders or conditions selected from dyslipidemia, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, low HDL levels, high LDL levels, and atherosclerosis and its sequelae. The combination therapy may make it possible to achieve therapeutic control using a reduced amount of one or both active ingredients and/or to achieve better lipid control than would be expected based on the control that is achieved when either of the compounds is used alone. The combination therapy may make it possible to achieve therapeutic control of one or more lipid disorders and diabetes. Preferred combinations include a compound of Claim I and one or more other compounds selected from a cholesterol absorption inhibitor, such as ezetimibe, a statin (e.g. simvastatin, atorvastatin, or rosuvastatin), an ACAT inhibitor, or another PPARα agonist, such as fenofibrate or another fibrate. Highly preferred combinations include combinations consisting essentially of a compound of this invention with a cholesterol absorption inhibitor (ezetimibe), or a compound of this invention with a statin (eg simvastatin), or a compound of this invention with both a statin and a cholesterol asorption inhibitor.

More generally, examples of therapeutic classes of compounds that may be administered in combination with a compound of Formula I, either separately or in the same pharmaceutical composition, include, but are not limited to:

(a) insulin sensitizers;
(b) antidiabetic compounds;
(c) cholesterol lowering agents;
(d) antiobesity compounds;
(e) anti-inflammatory compounds; and
(f) antihypertensives.

Examples of classes of compounds that may be administered in combination with compounds having Formula I include:

(a) PPARγ agonists and partial agonists, such as the glitazones (e.g. troglitazone, pioglitazone, englitazone, MCC-555, rosiglitazone, and the like);
(b) PPARα/γ dual agonists, such as KRP-297;
(c) other PPARα agonists, such as fenofibric acid derivatives, including gemfibrizol, clofibrate, fenofibrate, and bezafibrate,
(d) PPARδ agonists such as those disclosed in WO97/28149;
(e) biguanides, such as metformin and phenformin;
(f) protein tyrosine phosphatase-1B (PTP-1B) inhibitors;
(g) dipeptidyl peptidase IV (DP-IV) inhibitors;
(h) insulin or insulin mimetics;
(i) sulfonylureas, such as tolbutamide and glipizide, or related materials;
(j) α-glucosidase inhibitors (such as acarbose);
(k) glucagon receptor antagonists;
(l) glycogen phosphorylase inhibitors;
(m) 11-Beta-HSD type 1 enzyme inhibitors;
(n) 11-Beta-HSD type 1 receptor antagonists;
(o) exendin-4, exendin-3, GLP-1, GLP-1 mimetics, and GLP-1 receptor agonists, such as those disclosed in WO00/42026 and WO00/59887;
(p) GIP, GIP mimetics such as those disclosed in WO00/58360, and GIP receptor agonists;

(q) PACAP, PACAP mimetics, and PACAP receptor 3 agonists such as those disclosed in WO 01/23420;
(r) HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, itavastatin, rosuvastatin, ZD-4522, and other statins);
(s) Bile acid sequestrants (cholestyramine, colestipol, and dialkylaminoalkyl derivatives of a cross-linked dextran);
(t) nicotinyl alcohol, nicotinic acid or a salt thereof;
(u) ezetimibe and other inhibitors of cholesterol absorption;
(v) acyl CoA:cholesterol acyltransferase inhibitors (ACAT inhibitors); such as for example avasimibe;
(w) phenolic anti-oxidants, such as probucol;
(x) ileal bile acid transporter inhibitors;
(y) agents intended for use in the treatment of inflammatory conditions such as aspirin, non-steroidal anti-inflammatory drugs, glucocorticoids, azulfidine, and cyclooxygenase 2 selective inhibitors;
(z) antiobesity compounds such as fenfluramine, dexfenfluramine, phentermine, sibutramine, orlistat, neuropeptide Y5 inhibitors, and $\beta 3$ adrenergic receptor agonists;
(aa) thyroid hormone mimetics;
(bb) LXR agonists;
(cc) FXR agonists;
(dd) PLTP inhibitors;
(ee) CETP inhibitors;
(ff) glucocorticoids; and
(gg) TNF sequestrants.

The above combinations will generally include combinations of one compound of the present invention with one other active compound. However, it is contemplated that combinations may also include more than two active ingredients, selected from one or more compounds of the present invention and one or more other active compounds listed above. Non-limiting examples include combinations of one or more compounds having Formula I with two or more active compounds selected from insulin sensitizers; antidiabetic compounds; cholesterol lowering agents; antiobesity compounds; anti-inflammatory compounds; and antihypertensives.

Examples of combinations that may be appropriate for patients having Type 2 diabetes accompanied by dyslipidemia include one or more compounds having Formula I and one or more compounds selected from anti-diabetic compounds, including biguanides, sulfonylureas, other PPARγ agonists, PTP-1B inhibitors, DP-IV inhibitors, insulin, and anti-obesity compounds.

BIOLOGICAL ASSAYS

A) PPAR Binding Assays

For preparation of recombinant human PPARγ, PPARδ, and PPARα: Human $PPAR\gamma_2$, human PPARδ and human PPARα were expressed as gst-fusion proteins in *E. coli.* The full length human cDNA for $PPAR\gamma_2$ was subcloned into the pGEX-2T expression vector (Pharmacia). The full length human cDNAs for PPARδ and PPARα were subcloned into the pGEX-KT expression vector (Pharmacia). *E. coli* containing the respective plasmids were propagated, induced, and harvested by centrifugation. The resuspended pellet was broken in a French press and debris was removed by centrifugation at 12,000 X g. Recombinant human PPAR receptors were purified by affinity chromatography on glutathione sepharose. After application to the column, and one wash, receptor was eluted with glutathione. Glycerol (10%) was added to stabilize the receptor and aliquots were stored at -80°C.

For binding to PPARγ, an aliquot of receptor was incubated in TEGM (10 mM Tris, pH 7.2, 1 mM EDTA, 10% glycerol, 7 μL/100 mL ß-mercaptoethanol, 10 mM Na molybdate, 1 mM dithiothreitol, 5 μg/mL aprotinin, 2 μg/mL leupeptin, 2 μg/mL benzamidine and 0.5 mM PMSF) containing 0.1% non-fat dry milk and 10 nM [$^3H_2$] AD5075, (21 Ci/mmole), ± test compound as described in Berger et al (Novel peroxisome proliferator-activated receptor (PPARγ) and PPARδ ligands produce distinct biological effects. J. Biol. Chem. (1999), 274: 6718-6725.) Assays were

incubated for ~16 hr at 4°C in a final volume of 150 μL. Unbound ligand was removed by incubation with 100 μL dextran/gelatin-coated charcoal, on ice, for ~10 min. After centrifugation at 3000 rpm for 10 min at 4°C, 50 μL of the supernatant fraction was counted in a Topcount.

For binding to PPARδ, an aliquot of receptor was incubated in TEGM (10 mM Tris, pH 7.2, 1 mM EDTA, 10% glycerol, 7 μL/100 mL ß-mercaptoethanol, 10 mM Na molybdate, 1 mM dithiothreitol, 5 μg/mL aprotinin, 2 μg/mL leupeptin, 2 μg/mL benzamide and 0.5 mM PMSF) containing 0.1% non-fat dry milk and 2.5 nM [$^3H_2$]L-783483, (17 Ci/mmole), ± test compound as described in Berger et al (Novel peroxisome proliferator-activated receptorγ (PPARγ) and PPARδ ligands produce distinct biological effects.1999 J Biol Chem 274: 6718-6725). (L-783483 is 3-chloro-4-(3-(7-propyl-3-trifluoromethyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetic acid, Ex. 20 in WO 97/28137). Assays were incubated for ~16 hr at 4°C in a final volume of 150 μL. Unbound ligand was removed by incubation with 100 μL dextran/gelatin-coated charcoal, on ice, for ~10 min. After centrifugation at 3000 rpm for 10 min at 4°C, 50 μL of the supernatant fraction was counted in a Topcount.

For binding to PPARα, an aliquot of receptor was incubated in TEGM (10 mM Tris, pH 7.2, 1 mM EDTA, 10% glycerol, 7 μL/100 mL ß-mercaptoethanol, 10 mM Na molybdate, 1 mM dithiothreitol, 5 μg/mL aprotinin, 2 μg/mL leupeptin, 2 μg/mL benzamide and 0.5 mM PMSF) containing 0.1% non-fat dry milk and 5.0 nM [$^3H_2$](3-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)butyloxy))phenylacetic acid (34 Ci/mmole), ± test compound. This is a tritium labelled variant of Ex.62 in WO 97/28137. Assays were incubated for ~16 hr at 4°C in a final volume of 150 μL. Unbound ligand was removed by incubation with 100 μL dextran/gelatin-coated charcoal, on ice, for ~10 min. After centrifugation at 3000 rpm for 10 min at 4°C, 50 μL of the supernatant fraction was counted in a Topcount.

B). Gal-4 hPPAR Transactivation Assays

The chimeric receptor expression constructs, pcDNA3-hPPARγ/GAL4, pcDNA3-hPPARδ/GAL4, pcDNA3-hPPARα/GAL4 were prepared by inserting the yeast GAL4 transcription factor DBD adjacent to the ligand binding domains (LBDs) of hPPARγ, hPPARδ, hPPARα, respectively. The reporter construct, pUAS(5X)-tk-luc was generated by inserting 5 copies of the GAL4 response element upstream of the herpes virus minimal thymidine kinase promoter and the luciferase reporter gene.

pCMV-lacZ contains the galactosidase Z gene under the regulation of the cytomegalovirus promoter. COS-1 cells were seeded at 12 X 10^3 cells/well in 96 well cell culture plates in high glucose Dulbecco's modified Eagle medium (DMEM) containing 10% charcoal stripped fetal calf serum (Gemini Bio-Products, Calabasas, CA), nonessential amino acids, 100 units/ml Penicillin G and 100 mg/ml Streptomycin sulfate at 37 °C in a humidified atmosphere of 10% CO_2. After 24 h, transfections were performed with Lipofectamine (GIBCO BRL, Gaithersburg, MD) according to the instructions of the manufacturer. Briefly, transfection mixes for each well contained 0.48 µl of Lipofectamine, 0.00075 µg of pcDNA3-PPAR/GAL4 expression vector, 0.045 µg of pUAS(5X)-tk-luc reporter vector and 0.0002 µg of pCMV-lacZ as an internal control for transactivation efficiency. Cells were incubated in the transfection mixture for 5 h at 37° C in an atmosphere of 10% CO_2. The cells were then incubated for ~48 h in fresh high glucose DMEM containing 5% charcoal stripped fetal calf serum, nonessential amino acids, 100 units/ml Penicillin G and 100 mg/ml Streptomycin sulfate ± increasing concentrations of test compound. Since the compounds were solubilized in DMSO, control cells were incubated with equivalent concentrations of DMSO; final DMSO concentrations were ≤ 0.1%, a concentration which was shown not to effect transactivation activity. Cell lysates were produced using Reporter Lysis Buffer (Promega, Madison, WI) according to the manufacturer's instructions. Luciferase activity in cell extracts was determined using Luciferase Assay Buffer (Promega, Madison, WI) in an ML3000 luminometer (Dynatech Laboratories, Chantilly, VA). β-galactosidase activity was determined using β-D-galactopyranoside (Calbiochem, San Diego, CA).

C. In Vivo Studies

Male db/db mice (10-11 week old C57Bl/KFJ, Jackson Labs, Bar Harbor, ME) were housed 5/cage and allowed *ad lib.* access to ground Purina rodent chow and water. The animals, and their food, were weighed every 2 days and were dosed daily by gavage with vehicle (0.5% carboxymethylcellulose) ± test compound at the indicated dose. Drug suspensions were prepared daily. Plasma glucose, and triglyceride concentrations were determined from blood obtained by tail bleeds at 3-5 day intervals during the study period. Glucose, and triglyceride, determinations were performed on a Boehringer Mannheim Hitachi 911 automatic analyzer (Boehringer Mannheim, Indianapolis, IN) using heparinized plasma diluted 1:6 (v/v) with normal

saline. Lean animals were age-matched heterozygous mice maintained in the same manner.

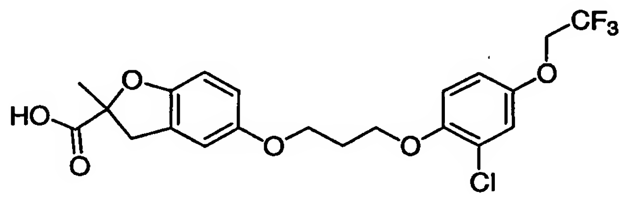
Male Golden Syrian hamsters weighing ~ 150 g are used to measure lipid modulation effects of test compounds. Hamsters are housed in boxes (5 per box), are fed a normal rodent chow diet, and are given free access to water. Compounds are suspended in 0.5% methylcellulose and gavaged daily to the hamsters for 9 days (10 hamsters per group). On the morning of the 10th day, the hamsters are euthanized with carbon dioxide, and blood samples are obtained via heart puncture. Serum levels of total cholesterol and triglycerides determined.

Mature male beagle dogs, weighing ~15 kg on average, are used to measure the lipid modulation effects of test compounds. Dogs are housed individually, are fed a cholesterol-free chow diet, and are given free access to water. Prior to the start of experiments, samples are taken weekly from the jugular vein and the serum cholesterol levels are determined. To test the effects of compounds on serum cholesterol, compounds are suspended in 0.5% methylcellulose and gavaged daily to the dogs for 2 weeks (5 dogs per group). Blood samples are taken during and after the dosing period, and serum levels of total cholesterol and triglycerides are determined.

TABLE OF COMPOUNDS

The table below illustrates compounds that were synthesized in accordance with the present invention. Detailed syntheses are provided in the Examples.

Example 1



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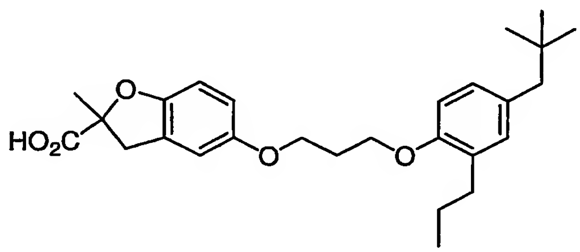

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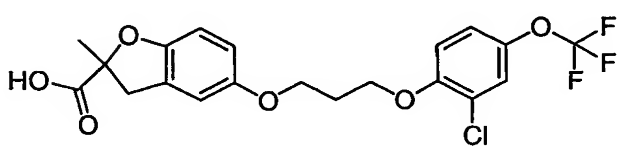

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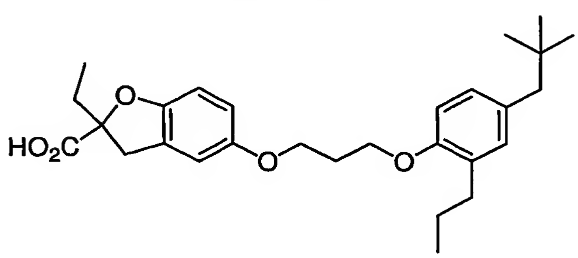

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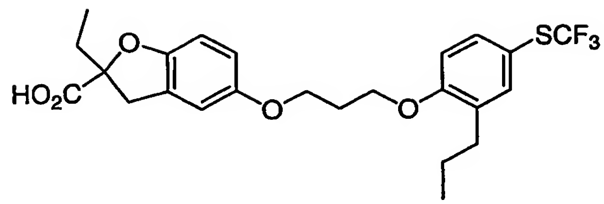

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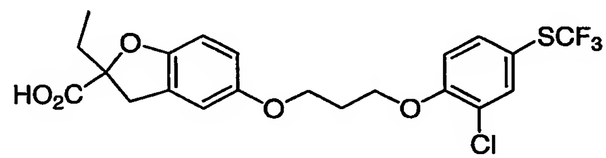

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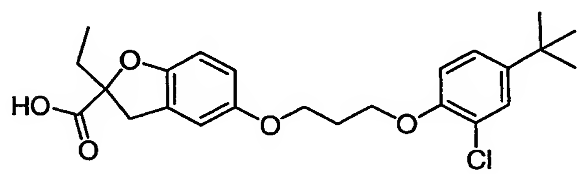

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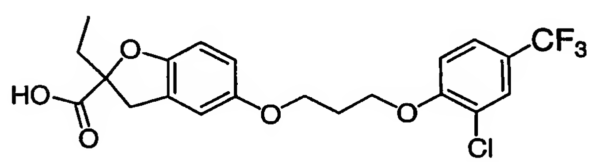

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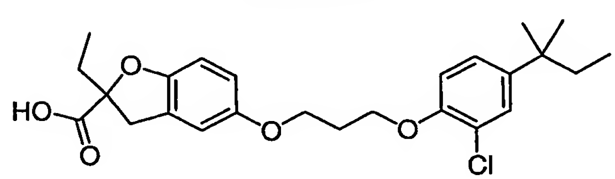

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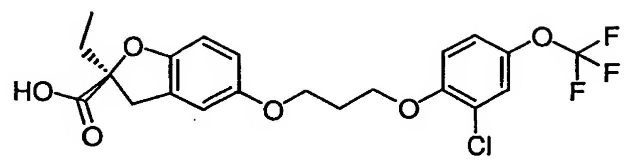

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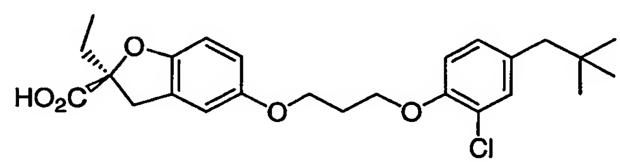

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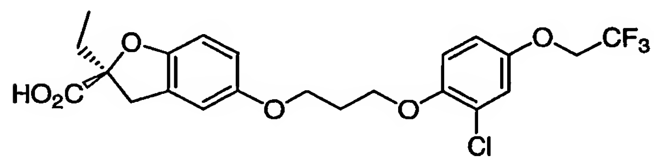

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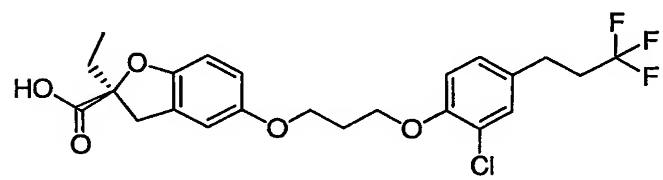

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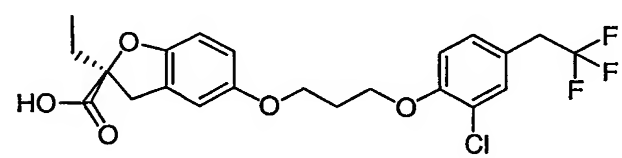
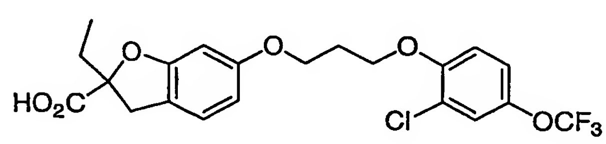
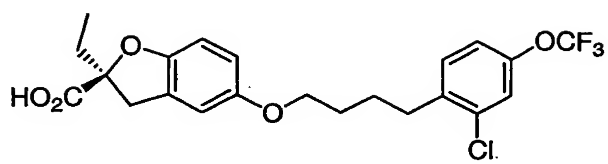


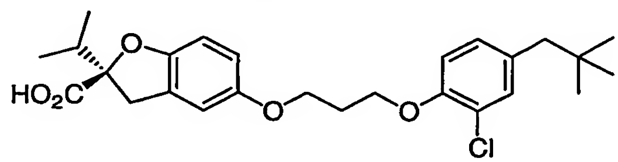
Example 15



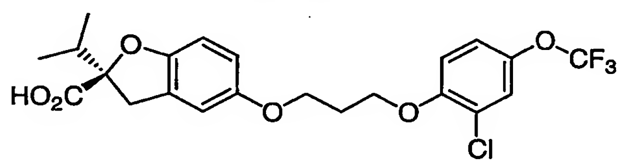
Example 16



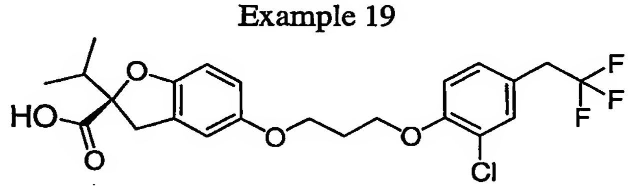
Example 17



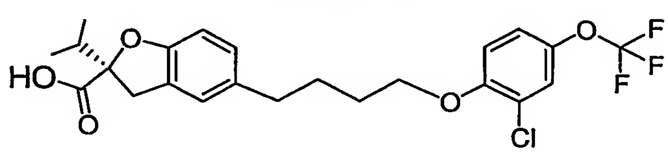
Example 18



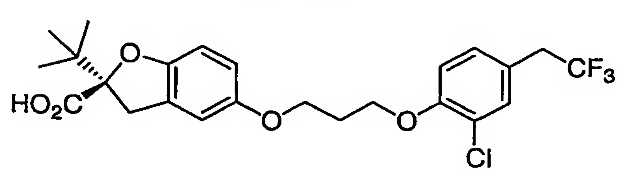
Example 19



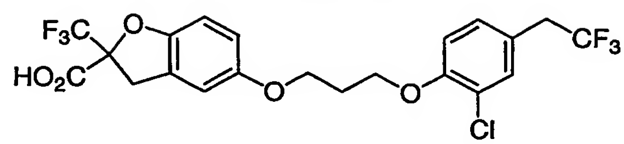
Example 20



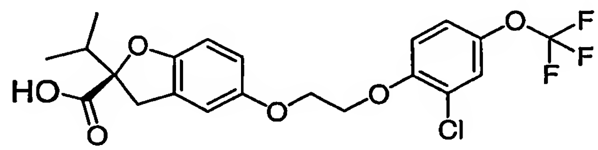
Example 21



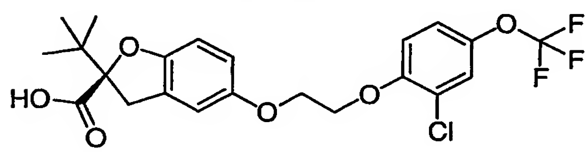
Example 22



Example 23



Example 24

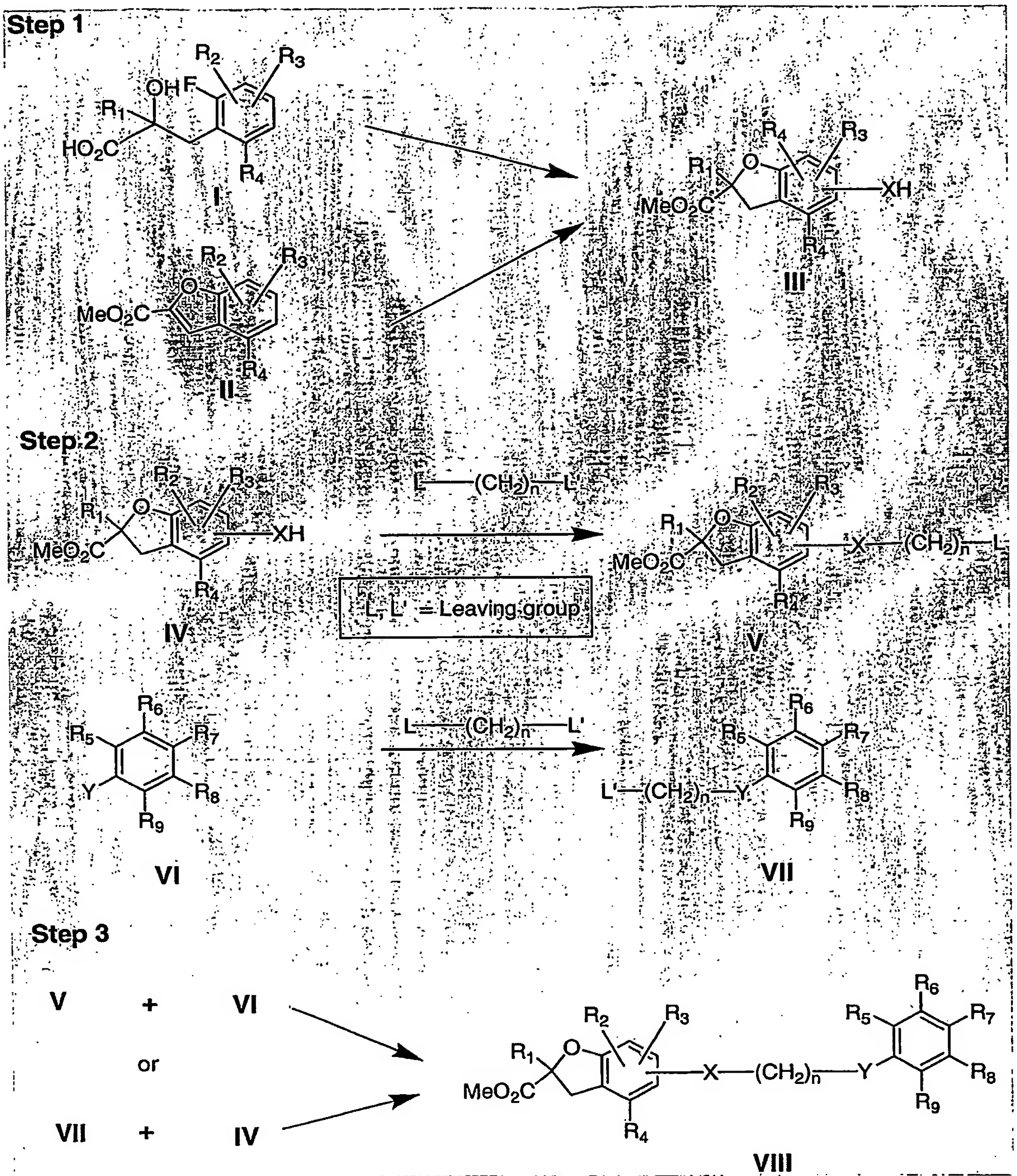


SYNTHETIC METHODS

The process for making the compounds of the instant invention is generally depicted in Scheme 1 below.

Note that the numbering of substituent groups used in the structures in Scheme I is different from the numbering in the generic description of the invention.

Scheme 1


Step 1
I
II
III
Step 2
IV
L—(CH2)n—L'
L, L' = Leaving group
V
VI
VII
Step 3
V + VI
or
VII + IV
VIII

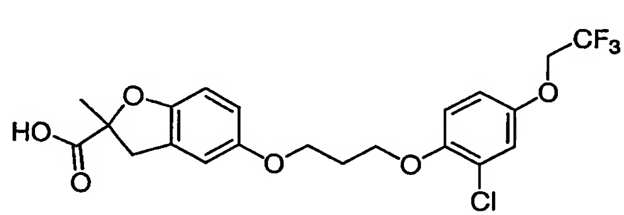
The appropriately substituted 2,3-dihydrobenzofuran-2-carboxylate of formula III may be synthesized by cyclization of the precursor I in the presence of a strong base (e.g. NaH) or by partial hydrogenation of benzofuran II followed by alkylation at the 2-position under standard ester enolate alkylation conditions. After compound of formula IV or VI is suitably connected with a tether, the assembly of the final compound may be performed by the coupling of compounds having formulae V and VI, or by the coupling of compounds having formulae VII and IV, where coupling is carried out in the presence of an inorganic base (e.g. cesium carbonate) in DMF or under palladium-catalyzed conditions(e.g. the Suzuki coupling conditions). L and L' are leaving groups well-known in the art, and preferably are independently selected from halogen, preferably iodine, bromine, or sulfonate such as methanesulfonate, or a boron group. Compounds having formulae I, II and VI may be commercially available, or prepared by published organic synthetic methods. The desired 2,3-dihydrobenzofuran-2-carboxylic acid VIII may be synthesized by ester hydrolysis of the compound having formula VIII under aqueous basic (e.g. aq. KOH) conditions.

EXAMPLES

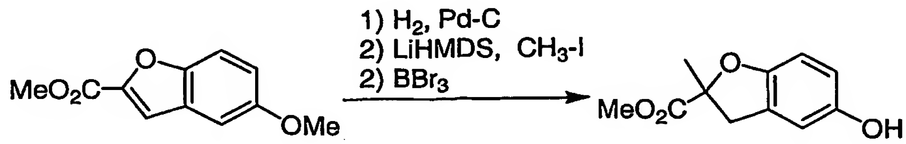
The following Examples are provided to illustrate the invention, including methods of making the compounds of the invention, and are not to be construed as limiting the invention in any manner. The scope of the invention is defined only in the appended claims.

EXAMPLE 1

5-{3-[2-Chloro-4-(2,2,2-trifluoro-ethoxy)-phenoxy]-propoxy}-2-methyl-2,3-dihydro-benzofuran-2-carboxylic acid



Step 1. 5-Hydroxy-2-methyl-2,3-dihydro-benzofuran-2-carboxylic acid methyl ester



5-Methoxy-benzofuran-2-carboxylic acid methyl ester (2.2 g, 10 mmol) and 10% Pd-C (0.44 g) in ethanol (50 mL) were agitated under hydrogen (45 psi) for 72 hrs. The reaction mixture was filtered and the filtrate was concentrated. The residue was chromatographed on silica gel eluting with 8:2 hexane:ethyl acetate to give 1.3 g 5-methoxy-2,3-dihydro-benzofuran-2-carboxylic acid methyl ester

To a solution of 5-methoxy-2,3-dihydro-benzofuran-2-carboxylic acid methyl ester (0.44 g, 2.0 mmol) and HMPA (0.20 mL) in THF (15 mL) at -78 °C was added LiHMDS (1M in THF, 3.0 mL, 3.0 mmol). After 15 min, methyl iodide (0.42 g, 3.0 mmol) was added and the reaction was gradually warmed to 25 °C overnight. The reaction mixture was diluted with ethyl acetate and washed with a saturated aqueous solution of NH_4Cl. The organic phase was dried and concentrated. The residue was chromatographed on silica gel eluting with 8:2 hexane:ethyl acetate to give 0.32 g 5-methoxy-2-methyl-2,3-dihydro-benzofuran-2-carboxylic acid methyl ester.

5-methoxy-2-methyl-2,3-dihydro-benzofuran-2-carboxylic acid methyl ester (0.32 g, 1.4 mmol) was dissolved in dichloromethane (10 mL) and cooled to 0 °C. A solution of boron tribromide in dichloromethane (1.0 M, 3.5 mL, 3.5 mmol) was added. After 1 hr at 0 °C, the reaction was diluted with dichloromethane and washed with brine. The organic phase was dried and concentrated. The residue was dissolved in 7:1 benzene:methanol (10 mL) and treated with $TMSCHN_2$ (1.0 M in hexane) until gas evolution ceased. Removal of the solvent gave a residue which was chromatographed on silica gel eluting with 7:3 hexane:ethyl acetate to give the title compound.

^{1}H NMR (500MHz, $CDCl_3$) δ 6.72 (d, J=8.5 Hz, 1H), 6.67 (d, J=3.0 Hz, 1H), 6.61 (dd, J=8.5, 3.0, 1H), 3.80 (s, 3H), 3.53 (d, J=16.0 Hz, 1H), 3.10 (d, J=16.0 Hz, 1H), 1.61 (s, 3H).

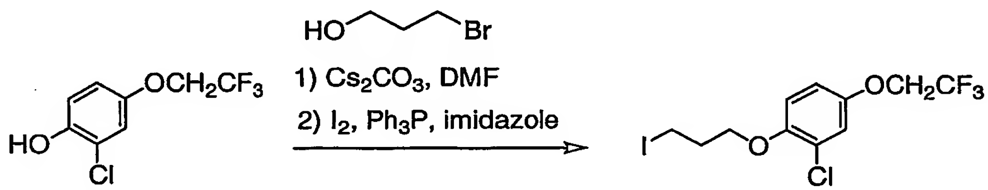
Step 2. 2-Chloro-4-(2,2,2-trifluoro-ethoxy)phenol

The title compound was prepared according to the following general procedure using 4-(trifluoroethoxy)phenol as the *para*-substituted phenol.

General procedure for the preparation of *ortho*-chlorinated phenols. To a solution of *para*-substituted phenol (5.0 mmol) and diisobutylamine (0.064 g, 0.5 mmol) in toluene (30 mL) was added SO_2Cl_2 (0.40 mL, 5.0 mmol) dropwise. After being stirred at 25 °C for 2 hr, the reaction was diluted with ethyl acetate, washed with brine and dried. Removal of solvent gave essentially pure *para*-substituted 2-chlorophenol.

^{1}H NMR (500MHz, $CDCl_3$) δ 6.99 (d, J= 2.5 Hz, 1H), 6.97 (d, J=8.5 Hz, 1H), 6.84 (dd, J=8.5, 2.5Hz, 1H), 5.33 (br. s, 1H), 4.30 (q, J=9.0 Hz, 2H).

Step 3. 2-Chloro-1-(3-iodo-propoxy)-4-(2,2,2-trifluoro-ethoxy)-benzene



The title compound was prepared according to the following general procedure employing 2-chloro-4-(2,2,2-trifluoroethoxy)phenol as the 2,4-disubstituted phenol.

General procedure for the preparation of 1-(3-iodo-propoxy)-2,4-disubstituted benzene from 2,4-disubstituted phenols. A mixture of 2,4-disubstituted phenol (10 mmol), 3-bromopropanol (4.2 g, 30 mmol) and Cs_2CO_3 (6.5 g, 20 mmol) in DMF (100 mL) was stirred at 60 °C for 5 hrs. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water (2 × 200 mL) and concentrated. The

residue was purified by chromatography on silica gel eluting with 1:1 hexane:ethyl acetate to give 3-(2,4-disubstituted phenoxy)-1-propanol. This product (8 mmol) was then dissolved in dichloromethane (50 mL) followed by addition of triphenylphosphine (2.5 g, 9.6 mmol), imidazole (1.1 g, 16 mmol) and iodine (2.4 g, 0.96 mmol). The reaction mixture was stirred at 25 °C for 30–60 min and then concentrated. The residue was triturated with 1:1 hexane:diethyl ether and filtered through silica gel to give essentially pure 1-(3-iodo-propoxy)-2,4-disubstituted-benzene

^{1}H NMR (500MHz, $CDCl_3$) δ 7.04 (d, J= 2.5 Hz, 1H), 6.94 (d, J=8.5 Hz, 1H), 6.84 (dd, J=8.5, 2.5 Hz, 1H), 4.33 (q, J=9.0 Hz, 2H), 4.08 (t, J=6.0 Hz, 2H), 3.42 (t, 6.5Hz, 2H), 2.3 (m, 2H).

Step 4. 5-{3-[2-Chloro-4-(2,2,2-trifluoro-ethoxy)-phenoxy]-propoxy}-2-methyl-2,3-dihydro-benzofuran-2-carboxylic acid.

The title compound was prepared according the following general procedure using the phenol prepared in Step 1 and the iodide prepared in Step 3.

<u>General procedure for the coupling of phenol with iodide and the subsequent hydrolysis of the coupling product.</u> A mixture of phenol (0.20 mmol), iodide (0.22 mmol) and Cs_2CO_3 (0.13 g, 0.40 mmol) in DMF (2.0 mL) was stirred at 25 °C for 6 h. The reaction mixture was diluted with ethyl acetate, washed with water and concentrated. The residue was purified by preparative TLC or flas chromatography on silica gel eluting with an appropriate ratio of hexane:ethyl acetate to give the coupling product. The coupling product (0.17 mmol) was dissolved in methanol (2.0 mL) and 2 *N* KOH (0.25 mL) was added. After 3 hrs at 25 - 60 °C, depending upon the hydrolytic stability of the ester group, the reaction mixture was acidified with 2 *N* HCl and extratracted with ethyl acetate. The organic phase was washed with brine , dried and concentrated . The residue was purified by preparative HPLC on a 100 × 20 mm YMC C-18 column using 10-100% gradient $CH_3CN–H_2O$

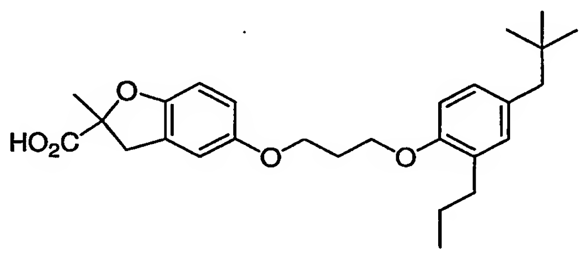
containing 0.1% TFA as the mobile phase to give the final 2,3-dihydro-benzofuran-2-carboxylic acid.

^{1}H NMR (500MHz, $CDCl_3$) δ 7.08 (d, J=3.0 Hz, 1H), 7.02 (d, J= 9.0 Hz, 1 H), 6.90 (dd, J= 9.0, 3.0 Hz, 1H), 6.7 (d, J=2.5 Hz, 1H), 6.70 (dd, J=9.0, 2.5 Hz, 1H), 6.66 (d, J=9.0 Hz, 1H), 4.46 (q, J= 8.5 Hz, 2H), 4.16 (t, J= 6.0 Hz, 2H), 4.12 (t, J-6.0 Hz, 2H), 3.53(d, J= 16.5 Hz, 1H), 3.11 (d, J=16.5 Hz, 1H), 2.19 (quintet, J= 6.0 Hz, 2H), 1.63 (s, 3H).

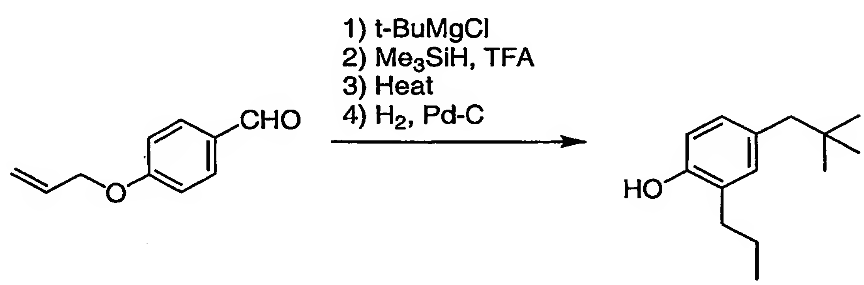
MS (ESI, m/z): 460.1 (M^+).

Example 2

5-{3-[4-(2,2-Dimethyl-propyl)-2-propyl-phenoxy]-propoxy}-2-methyl-2,3-dihydro-benzofuran-2-carboxylic acid



Step 1. 4-(2,2-Dimethyl-propyl)-2-propyl-phenol



To a solution of 4-allyoxybenzaldehyde (1.38 g, 10 mmol) in THF (50 mL) cooled at –78 °C was added a solution t-butylmagnesium chloride in THF (1M, 11 mL, 11 mmol). The reaction was warmed to 25 °C and quenched by addition of

saturated aqueous NH_4Cl. The organic phase was separated , dried and concentrated. The residue was purified by chromatography on silica gel eluting with 9:1 hexane: ethyl acetate to give 1.2 g 1-(4-allyloxyphenyl)-2,2-dimethylpropan-1-ol.

1-(4-Allyloxyphenyl)-2,2-dimethylpropan-1-ol (1.2 g, 6.1 mmol) and trimethylsilane (mL, 61.0 mmol) were dissolved in dichlorormethane (5.0 mL) and trifluoroacetic acid (2.1 g, 18.3 mmol) was added at 0 °C. After 30 min, the reaction mixture was concentrated to give esentially pure 1-allyloxy-4-neopentylbenzene. The crude product was dissolved in 1,2,4-trichlorobenzene (5.0 mL) and the solution was heated to reflux for 4 hrs. Removal of solvent and chromatography of the residue on silica gel eluting with 9:1 hexane:ethyl acetate gave 0.70 g 2-allyl-4-(2,2-dimethyl-propyl)phenol.

A mixture of 2-allyl-4-(2,2-dimethyl-propyl)phenol (0.70 g, 3.4 mmol) and 10% palladium on carbon (0.14 g) in ethyl acetate was stirried under hydrogen (1 atm) for 1 h. The reaction mixture was filtered and the filtrate was concentrated to give the title compound.

^{1}H NMR (500MHz, $CDCl_3$) δ 6.89 (d, J=2.5 Hz, 1H), 6.86 (dd, J=8.5, 2.5 Hz, 1H), 6.69 (d, J=8.5 Hz, 2.60 (t, J= 6.5 Hz, 2H), 1.67 (sixtet, J= 6.5 Hz, 2H), 1.0 (t, J=6.5 Hz,3H), 0.95 (s, 9H).

Step 2. 1-(3-iodo-propoxy)- 4-(2,2-dimethyl-propyl)-2-propyl-benzene

The title compound was prepared following the general procedure described in Example 1, Step 3 using the phenol prepared in Step 1 as the 2,4-disubstituted phenol..

^{1}H NMR (500MHz, CDCl3) δ 7.15 (d, J=2.5 Hz, 1H), 6.97 (dd, J=8.5, 2.5 Hz, 1H), 6.86 (d, J=8.5 Hz, 1H), 4.20 (t, J=6.5 Hz, 2H), 3.41 (t, J=6.5 Hz, 2H),), 2.60 (t,

J=6.5Hz, 2H), 2.42 (s, 2H), 2.13 (quintet, J=6.5 Hz, 2H), 1.52 (m, 2H), 1.02 (t, J=6.5Hz, 3H), 0.89 (t, J=6.5 Hz, 3H), 0.88 (s, 9H).

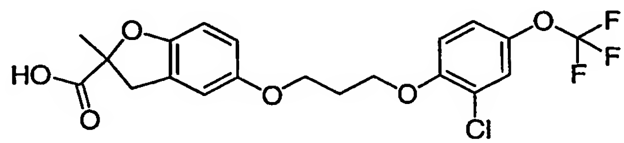
Step 3. 5-{3-[4-(2,2-Dimethyl-propyl)-2-propyl-phenoxy]-propoxy}-2-methyl-2,3-dihydro-benzofuran-2-carboxylic acid

The title compound was prepared following the general procedure described in Example 1, Step 4, employing the intermediate prepared in Example 1, Step 1 as the phenol and the iodide prepared in Step 2.

^{1}H NMR (500MHz, CD_3OD) δ 6.83-6.88 (m, 2H), 6.76-6.80 (m, 2H), 6.64-6.70 (m, 2H), 4.10 (t, J= 6.0 Hz, 4H), 3.53 (d, J= 16.5Hz, 1H), 3.08 (d, J=16.5Hz, 1H), 2.53 (t, J= 7.5 Hz, 2.38 (s, 2H), 2.17 (quintet, J= 6.0 Hz, 2H), 1.61 (s, 3H), 1.55 (m, 2H), 0.87 (t, J=6.5 Hz, 3H), 0.86 (s, 9H).
MS (ESI, m/z): 441.3 (M^++1).

Example 3

5-[3-(2-Chloro-4-trifluoromethoxy-phenoxy)-propoxy]-2-methyl-2,3-dihydro-benzofuran-2-carboxylic acid



Step 1. 2-chloro-4-(trifluoromethoxy)phenol

The title compound was prepared according to the general procedure described in Example 1, Step 2 using 4-trifluoromethoxyphenol as *para*-substituted phenol.

^{1}H NMR (500MHz, $CDCl_3$) δ 7.30 (d, J=2.5 Hz, 1H), 7.15 (dd, J=9.0, 2.0 Hz, 1H), 7.10 (d, J=9.0 Hz, 1H), 4.30 (br. s, 1H).

Step 2. 1-(3-iodo-propoxy)-2-chloro-4-(trifluoromethoxy)-benzene

The title compound was prepared following the general procedure described in Example 1, Step 3 using the phenol prepared in Step 1 as the 2,4-disubstituted phenol.

^{1}H NMR (500MHz, $CDCl_3$) δ 7.31 (d, J=2.5 Hz, 1H), 7.16 (dd, J=9.0, 2.0Hz, 1H), 7.10 (d, J=9.0 Hz, 1H), 4.14 (t, J=6.0 Hz, 2H), 3.42 (t, 6.5Hz, 2H) 2.30 (m, 2H).

Step 3. 5-[3-(2-Chloro-4-trifluoromethoxy-phenoxy)-propoxy]-2-methyl-2,3-dihydro-benzofuran-2-carboxylic acid

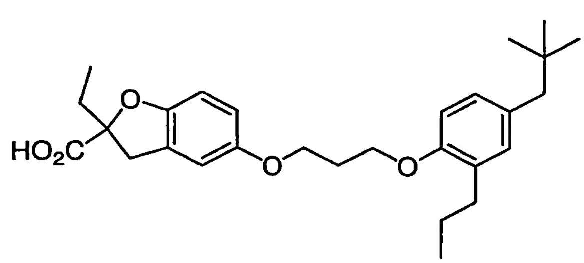
The title compound was prepared following the general procedure described in Example 1, Step 4, using the the intermediate prepared in Example 1, Step 1 as the phenol and the iodide prepared in Step 2.

^{1}H NMR (500MHz, CD_3OD) δ 7.34 (d, J=2.5 Hz, 1H), 7.19 (dd, J=9.0, 2.0 Hz, 1H), 7.15 (d, J=9.0 Hz, 1H), 6.80 (d, J=2.5 Hz, 1H), 6.70 (dd, J=8.5, 2.5 Hz, 1H), 6.66 (d, J=8.5 Hz, 1H), 4.25 (t, J=6.0 Hz, 2H), 4.14 (t, J=6.0 Hz, 2H), 3.54 (d, J=16.5 Hz, 1H), 3.11 (d, J=16.5 Hz, 1H), 2.27-2.22 (quintet, J=6.0 Hz, 2H), 1.63 (s, 3H).

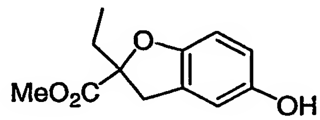
MS (ESI, m/z): 447.8 (M^++1)

Example 4

5-{3-[4-(2,2-Dimethyl-propyl)-2-propyl-phenoxy]-propoxy}-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid



Step1. 2-Ethyl-5-hydroxy-2,3-dihydro-benzofuran-2-carboxylic acid methyl ester



The title compound was prepared following the procedure described in Example 1, Step 1, employing ethyl iodide instead of methyl iodide as the electrophile.

^{1}H NMR (500MHz, CDCl3) δ 6.72 (d, J=8.5 Hz, 1H), 6.67 (d, J=3Hz, 1H), 6.61 (dd, J=8.5, 3.0, 1H), 3.80 (s, 3H), 3.54 (d, J=14.0 Hz, 1H), 3.16 (d, J=14.0 Hz, 1H), 2.05 (m, 2H), 1.0 (t, J=7.5 Hz, 3H) .

MS (ESI, m/z): 223 (M^++1) .

Step 2. 5-{3-[4-(2,2-Dimethyl-propyl)-2-propyl-phenoxy]-propoxy}-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid.

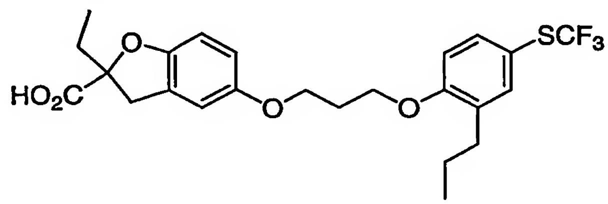
The title compound was prepared following the general procedure described in Example 1, Step 4, employing the phenol prepared in Step 1 and the intermediate prepared in Example 2, Step 2 as the iodide.

^{1}H NMR (500MHz, $CDCl_3$) δ 6.88 (dd, J= 2H, 1H), 6.76-6.80 (m, 2H), 6.64-6.70 (m, 2H), 4.10 (t, J= 6.0 Hz, 4H), 3.53 (d, J= 16.5 Hz, 1H), 3.08 (d, J=16.5 Hz, 1H), 2.53 (t, J= 7.5Hz, 2.38 (s, 2H), 2.17 (quintet, J= 6.0 Hz, 2H), 1.55 (m, 2H), 0.86 (s, 9H).

MS (ESI, m/z): 441.3 (M^++1).

Example 5

2-Ethyl-5-[3-(2-propyl-4-trifluoromethylsulfanyl-phenoxy)-propoxy]-2,3-dihydro-benzofuran-2-carboxylic acid



Step 1. 2-Propyl-4-(trifluoromethylsulfanyl)phenol

A mixture of 4-(trifluoromethylsulfanyl)phenol (1.9 g, 10 mmol), allyl brimide (1.8 g, 15 mmol) and Cs_2CO_3 (6.5 g, 20 mmol) in DMF, 80 mL) was stirred for 2 hrs at 50 °C. The reaction was diluted with ethyl acetate and washed with water. The organic phase was dried and concentrated to give essentially pure allyl 4-(trifluoromethylsulfanyl)phenyl ether.

The allyl ether (2.3 g, 10 mmol) was dissolved in 1,2,4-trichlorobenzene (10 mL) and the solution was heated at reflux for 4 hrs. The reaction was cooled and poured on the top of a silica gel column. Sequential elution with 100% hexane and 9:1 hexane:ethyl acetate gave 1.8 g 2-allyl-4-(trifluoromethylsulfanyl)phenol. This compound was hydrogenated (1 atm hydrogen) in ethyl acetate (20 mL) in the presence of 10% Pd-C (0.36 g) to give 1.8 g of the title compound.

Step 2. 1-(3-iodo-propoxy)-2-propyl-4-(trifluoromethylsulfanyl)-benezene

The title compound was prepared following the general procedure described in Example 1, Step 3 employing the phenol prepared in Step 1 as the 2,4-disubstituted phenol.

^{1}H NMR (500MHz, CDCl3) δ 7.45 (dd, J= 8.5, 2.5 Hz, 1H), 7.38 (d, J=2.5 Hz, 1H), 7.00 (d, J=8.5 Hz, 1H), 4.15 (t, J=6.5 Hz, 2H), 3.40 (t, J=6.5 Hz, 2H), 2.59 (t, J= 7.5 Hz, 2H), 2.22 (quintet, J=6.5 Hz, 2H) 1.57 (m, 2H), 0.89 (t, J=7.5Hz, 3H).

Step 3. 2-Ethyl-5-[3-(2-propyl-4-trifluoromethylsulfanyl-phenoxy)-propoxy]-2,3-dihydro-benzofuran-2-carboxylic acid.

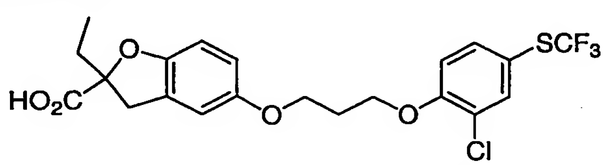
The title compound was prepared following the general procedure decribed in Example 1, Step 4 using the intermediate prepared in Example 4, Step 1 as the phenol and the iodo compound prepared in Step 2.

^{1}H NMR (500MHz, $CDCl_3$) δ 7.46 (dd, J= 8.5, 2.5, 1H), 7.38 (d, 2.5 Hz, 1H), 7.01 (d, J=8.5 Hz, 1H), 6.78 (br.s, 1H), 6.66-6.71 (m, 2H), 4.21(t, J=6.0Hz, 2H), 4.11 (t, J=6.0 Hz, 2H), 3.48 (d, J= 16.5 Hz, 1H), 3.15 (d, J= 16.5 Hz, 1H), 2.58 (t, J= 7.5Hz, 2H), 2.22 (quintet, J= 6.0 Hz, 2H), 2.03 (dq, J=14.5, 7.5 Hz, 1H), 1.93 (dq, J=14.5, 7.5 Hz, 1H), 1.56 (sixtet, J= 7.5 Hz, 2H), 0.97 (t, J=7.5 Hz,3H), 0.89 (t, J=7.5 Hz, 3H).

MS (ESI, m/z): 507.2 (M^++Na).

Example 6

5-[3-(2-Chloro-4-trifluoromethylsulfanyl-phenoxy)-propoxy]-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid



Step 1. 2-Chloro-4-(trifluoromethylsulfanyl)-phenol

The title compound was prepared following the procedure described in Example 1, Step 2 using 4-(trifluoromethylsulfanyl)phenol as the *para*-substituted phenol.

Step 2. 2-Chloro-1-(3-iodo-propoxy)-4-(trifluoromethylsulfanyl)-benzene

The title compound was prepared following the general procedure described in Example 1, Step 3, using the phenol prepared in Step 1 as the 2,4-disubstituted phenol.

Step 3. 5-[3-(2-Chloro-4-trifluoromethylsulfanyl-phenoxy)-propoxy]-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid

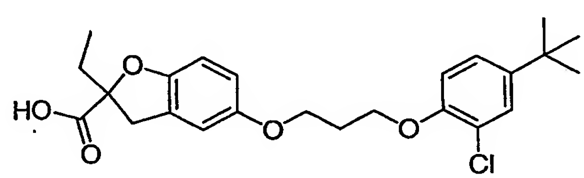
The title compound was prepared following the general procedure described in Example 1, Step 4 employing the phenol prepared in Example 4, Step 1 and the iodide prepared in Step 2.

^{1}H NMR (500MHz, $CDCl_3$) δ 7.68 (d, J= 2.0 Hz, 1H), 7.58 (dd, J=8.0, 2.0 Hz, 1H), 7.18 (d, 8.0Hz, 1H), 6.79 (d, J=1.5Hz, 1H), 6.70 (dd, J= 9.0, 1.5 Hz, 1H), 6.67 (d, J=9.0 Hz, 1H), 4.29 (t, J=6.0 Hz, 2H), 4.13 (t, J=6.0 Hz, 2H), 3.47 (d, J= 16.5 Hz, 1H), 3.15 (d, J=16.5 Hz, 1H), 2.54 (quintet, J=6.5 Hz, 2H), 2.03 (dq, J=14.5, 7.5 Hz, 1H), 1.93 (dq, J=14.5, 7.5 Hz, 1H), 0.99 (t, J=7.5 Hz, 3H).

MS (ESI, m/z): 499.1 (M^++Na).

Example 7

5-[3-(4-*tert*-Butyl-2-chloro-phenoxy)-propoxy]-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid



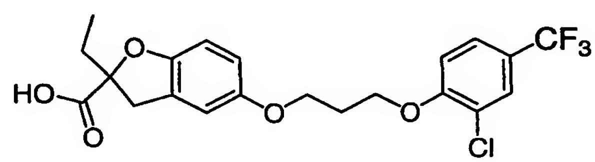
The title compound was prepared following the general procedures described Example 1, Step 3 and Step 4, employing 2-chloro-4-*tert*-butylphenol instead of 2-chloro-4-(trifluoroethoxy)phenol for the preparation of the iodide and the intermediate prepared in Example 4, Step 1 as the phenol for coupling with the iodide.

^{1}H NMR (500MHz, CD_3OD) δ 7.35 (d, J=2.5 Hz, 1H), 7.25 (dd, J=8.5, 2.0 Hz, 1H), 6.98 (d, J=8.5 Hz, 1H), 6.80 (d, J=2.5 Hz, 1H), 6.71 (dd, J_1=8.5, 2.5 Hz, 1H), 6.67 (d, J=8.5 Hz, 1H), 4.18 (t, J=6.0 Hz, 2H), 4.13 (t, J=6.0 Hz, 2H), 3.47 (d, J=16.0 Hz, 1H), 3.16 (d, J=16.0 Hz, 1H), 2.20 (quintet, J= 6.0 Hz, 2H), 2.05 (dq, J=14.0, 7.5Hz, 1H), 1.94 (dq, J=14.0, 7.5Hz,1H), 1.28 (s, 9H), 0.99 (t, J=7.5 Hz, 3H).

MS (ESI, m/z): 455.1 (M^++Na)

Example 8

5-[3-(2-Chloro-4-trifluoromethyl-phenoxy)-propoxy]-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid



Step 1. 2-Chloro-1-(3-iodo-propoxy)-4-(trifluoromethyl)-benzene

The title compound was prepared following the general procedure described in Example 1, Step 3, employing 2-chloro-4-(trifluoromethyl)phenol as the 2,4-disubstituted phenol.

Step 2. 5-[3-(2-Chloro-4-trifluoromethyl-phenoxy)-propoxy]-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid.

The title compound was prepared following the general procedure described in Example 1, Step 4 employing the phenol prepared in Example 3, Step 1 and the iodide prepared in Step 1.

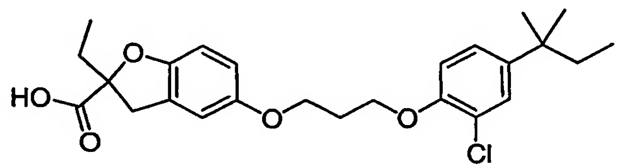
^{1}H NMR (500MHz, CD_3OD) δ 7.66 (d, J=2.0 Hz, 1H), 7.56 (dd, J=9.0, 2.0 Hz, 1H), 7.23 (d, J=9.0 Hz, 1H), 6.80 (d, J=2.5 Hz, 1H), 6.71 (dd, J=8.5, 2.5 Hz, 1H), 6.68 (d, J=8.5 Hz, 1H), 4.31 (t, J=6.0 Hz, 2H), 4.14 (t, J=6.0 Hz, 2H), 3.48 (d, J=16.5 Hz, 1H),

3.16 (d, J=16.5 Hz, 1H), 2.29-2.24 (m, 2H), 2.08-2.00 (m, 1H), 1.97-1.90 (m, 1H), 0.99 (t, J=7.5 Hz, 3H).

MS (ESI, m/z): 445.8 (M^{+}+1).

Example 9

5-{3-[2-Chloro-4-(1,1-dimethyl-propyl)-phenoxy]-propoxy}-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid



Step 1. 2-Chloro-1-(3-iodo-propoxy)-4-(1,1-dimethyl-propyl)-benzene

The title compound was prepared following the general procedure described in Example 1, Step 3 employing 2-chloro-4-(1,1-dimethyl-propyl)-phenol as the 2,4-disubstituted phenol.

Step 2. 5-{3-[2-Chloro-4-(1,1-dimethyl-propyl)-phenoxy]-propoxy}-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid

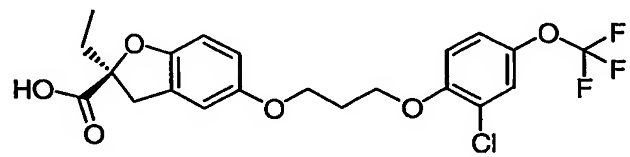
The title compound was prepared following the general procedure described in Example 1, Step 4 employing the phenol prepared in Example 4, Step 1 and the iodide prepared in Step 1.

^{1}H NMR (500MHz, CD_3OD) δ 7.29 (d, J=2.5 Hz, 1H), 7.19 (dd, J_1=8.5, 2.5 Hz, 1H), 6.98 (d, J=8.5 Hz, 1H), 6.80 (d, J=2.0 Hz, 1H), 6.70 (dd, J=9.0, 2.5 Hz, 1H), 6.67 (d, J=9.0 Hz, 1H), 4.19 (t, J=6.0 Hz, 2H), 4.13 (t, J=6.0 Hz, 2H), 3.48 (d, J=16.0 Hz, 1H), 3.16 (d, J=16.0 Hz, 1H), 2.20 (quintet, J=6.0Hz, 2H), 2.03 (dq, J=14.0, 7.5Hz, 1H), 1.93 (dq, J=14.0, 7.5Hz, 1H), 1.62 (q, J=7.5 Hz, 2H), 1.24 (s, 6H), 0.99 (t, J=7.5 Hz, 3H), 0.67 (t, J=7.5 Hz, 3H).

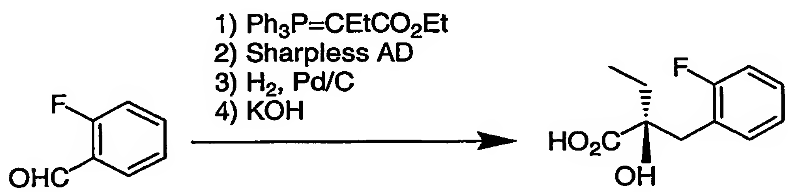
MS (ESI, m/z): 447.0 (M^{+}+1).

Example 10

(2*S*)-5-[3-(2-Chloro-4-trifluoromethoxy-phenoxy)-propoxy]-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid



Step 1. (2*S*)-2-(2-Fluoro-benzyl)-2-hydroxy-butyric acid



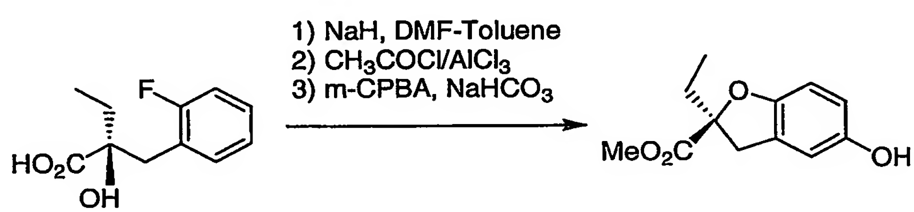
A solution of 2-fluorobenzaldehyde (6.2 g, 50 mmol) and ethyl 2-(triphenylphosphoranylidene)butanoate (18.8 g, 50 mmol) in THF (200 mL) was refluxed for 2 hrs. The reaction mixture was concentrated and the residue was triturated with 1:1 hexane:ethyl acetate. The precipitate was removed by filtration through silica gel and the filtrate was concentrated. The residue was purified by chromatography on silica gel eluting with 8:2 hexane:ethyl acetate to give ethyl (*E*)-2-ethyl-3-(2-fluorophenyl)propenoate.

Ethyl (*E*)-2-ethyl-3-(2-fluorophenyl)propenoate (4.4 g, 20 mmol), AD-mix-β (28.0 g) and methylsulfonamide (1.9 g, 2.0 mmol) were mixed in 1:1 *t*-BuOH:H_2O (200 mL). The resulting mixture was stirred at 4 °C for 2 days and quenched by addition of an aqueous solution of Na_2SO_3 (2 *N*, 20 mL). The mixture was diluted with ethyl acetate (200 mL), washed with brine (2 × 100 mL) and dried. Removal of solvent gave ethyl (2*S*, 3*S*)-2-ethyl-3-(2-fluorophenyl)-2,3-dihydroxypropanoate with 97% ee, as determined by HPLC on a Chiracel OD column using 30% isopropanol in heptane as the mobile phase.

Ethyl (2*S*, 3*S*)-2-ethyl-3-(2-fluorophenyl)-2,3-dihydroxypropanoate (5.2 g, 20 mmol), 10% palladium on carbon (2.5 g) and concentrated sulfuric acid (0. 53 mL, 10 mmol) were mixed in acetic acid (100 mL). The reaction mixture was hydrogenated at 45 psi for 48 hrs. Sodium acetate (1.7 g, 20 mmol) was added and the reaction mixture was stirred for 10 min before it was filtered through silica gel. Concentration of the filtrate gave essentially pure ethyl (2*S*)-2-(2-Fluoro-benzyl)-2-hydroxy-butyrate, which was hydrolyzed with KOH (2 *N*, 25 mL) in methanol (150 mL) to give the title compound.

^{1}H NMR (600MHz, $CDCl_3$) δ 7.22-7.30 (m, 2H), 7.08 (t, J=7.8 Hz, 1H), 7.03 (dd, J= 7.8, 9.0 Hz, 1H), 3.17 (d, J=14.0 Hz, 1H), 3.08 (d, J=14 Hz, 1H), 2.03 (dq, J=13.8, 7.8 Hz, 1H), 1.76 (dq, J= 13.8, 7.8 Hz, 1H), 0.97 (t, J=7.8 Hz, 3H).

Step 2. 2-Ethyl-5-hydroxy-2,3-dihydro-benzofuran-2-carboxylic acid methyl ester



To a solution of the acid from step 1 (4.0 g , ca. 20 mmol) in 1:4 DMF:toluene (100 mL) was added 60% NaH in mineral oil (1.76 g, 44 mmol) in 3 portions. The reaction mixture was stirred at 110 °C under N_2 for 4 hrs. The reaction was cooled to room temperature and poured into cold water (100 mL). The aqueous layer was washed with hexane (50 mL), acidified with 2 *N* aqueous HCl and extracted with ethyl acetate (3 × 50 mL). The extracts were washed with brine (50 mL), dried and concentrated. The residue was dissolved in 7:1 benzene:MeOH (80 mL) and treated with $TMSCHN_2$ (1M in hexane) until gas evolution ceased. The reaction was concentrated and the residue was chromatographed on silica gel eluting with 85:15

hexane:ethylacetate to give methyl (2*S*)-2-ethyl-2,3-dihydro-benzofuran-2-carboxylate.

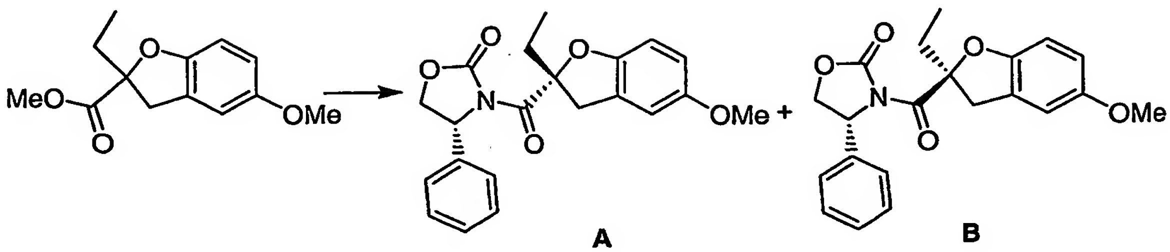
Methyl (2*S*)-2-ethyl-2,3-dihydro-benzofuran-2-carboxylate(3.1 g, 15 mmol) was mixed with acetyl chloride (3.5 g, 45 mmol) and aluminum chloride (6.0 g, 45 mmol) in dichloromethane (100 mL). The reaction mixture was stirred at 25 °C for 1 hr and then poured into 1 *N* aqueous HCl (100 mL). The organic layer was separated and the aqueous phase was extracted with dichloromethane (50 mL). The combined extracts were washed with brine and concentrated to give essentially pure methyl (2*S*)-5-acetyl-2-ethyl-2,3-dihydro-benzofuran-2-carboxylate.

Methyl (2*S*)-5-acetyl-2-ethyl-2,3-dihydro-benzofuran-2-carboxylate (3.8 g, ca. 15 mmol), *m*-chloroperbenzoic acid (70%, 7.7 g, 30 mmol) and $NaHCO_3$ (3.8 g, 45 mmol) in dichloromethane (150 mL) was stirred under reflux for 2 hrs. The reaction mixture was washed successively with saturated aqueous sodium sulfite (100 mL) and aqueous $NaHCO_3$ (2 × 100 mL). After removal of solvent, the residue was dissolved in methanol (100 mL) and treated with aqueous KOH (5 *N*, 3 mL) at 0 °C for 5 min. The reaction was neutralized with excess solid sodium bicarbonate, filtered and concentrated. The residue was purified by chromatography on silica gel eluting with 8:2 hexane:ethyl acetate to give the title compound.

^{1}H NMR (500MHz, $CDCl_3$) δ 6.72 (d, J=8.5 Hz, 1H), 6.67 (d, J=3Hz, 1H), 6.61 (dd, J=8.5, 3.0, 1H), 3.80 (s, 3H), 3.54 (d, J=14.0 Hz, 1H), 3.16 (d, J=14.0 Hz, 1H), 2.05 (m, 2H), 1.0 (t, J=7.5 Hz, 3H).

MS (ESI, m/z): 223 (M^++1).

Step 3: Determination of the absolute stereochemistry



The racemate intermediate from example 4, step 1 was converted to a separable diastereoisomeric mixture (2*R*)-2-phenyloxazolinone amide A and B. The stereochemistry at the chiral center of of the isomer A was found to be *R* by X-ray crystallography. Since isomer B can be derived from the phenol prepared in step 2, it can be concluded that the phenol obtained in step 2 has *S* configuration at its chiral center.

X-Ray crystal structure of isomer A

Crystals suitable for diffraction studies were grown from a mixture of acetonitrile/water. The crystals obtained are orthorhombic with space group $P2_12_12_1$ and cell constants of $a = 6.108(2)$, $b = 11.040(3)$, $c = 26.546(7)$ Å, with $V = 1790(1)$ Å^3, and $Z = 4$. The calculated density is 1.363 g cm^{-3}.

All diffraction measurements were made using monochromatized Mo K_α radiation ($\lambda = 0.71073$ Å) on a CCD area-detector equipped diffractometer, at $T = 100$ K, to a θ limit of 26.39°. There are 3674 unique reflections out of 19712 measured with 2464 observed at the $I \geq 2\sigma(I)$ level.The structure was solved by direct methods and refined using full-matrix least-squares on F^2 using 246 parameters and all unique reflections. The refinement converged with agreement statistics of $R = 0.041$, $wR = 0.066$, $S = 0.93$ with $(\Delta/\sigma)_{max} = 0.01$.

A computer-generated perspective view of isomer A is shown in Figure 2. Lists of interatomic distances and angles are given in Tables 1 and 2, respectively.

Figure 2

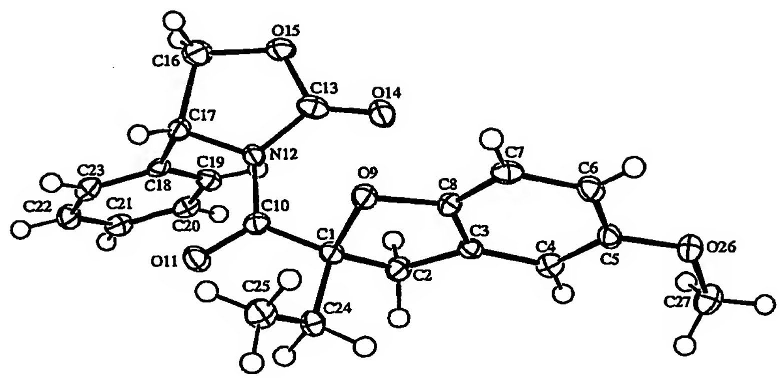


Table 1 Interatomic Distances (Å)

O9—C8	1.396(2)	C21—C22	1.378(3)
O9—C1	1.460(2)	C21—C20	1.393(3)
O15—C13	1.348(3)	C3—C2	1.510(3)
O15—C16	1.455(3)	C18—C23	1.388(3)
O26—C5	1.384(2)	C18—C19	1.390(3)
O26—C27	1.440(3)	C18—C17	1.518(3)
O11—C10	1.224(2)	C20—C19	1.387(3)
O14—C13	1.194(3)	C2—C1	1.553(3)
C4—C5	1.387(3)	C23—C22	1.388(3)
C4—C3	1.395(3)	N12—C10	1.393(3)
C13—N12	1.406(3)	N12—C17	1.478(3)
C8—C7	1.378(3)	C25—C24	1.528(3)
C8—C3	1.379(3)	C24—C1	1.535(3)
C7—C6	1.397(3)	C1—C10	1.527(3)
C5—C6	1.392(3)	C16—C17	1.530(3)

Table 2. Interatomic Angles (deg.)

C8—O9—C1	105.38(16)	C3—C2—C1	99.71(16)
C13—O15—C16	110.84(18)	C22—C23—C18	120.6(2)
C5—O26—C27	116.48(17)	C10—N12—C13	130.33(18)
C5—C4—C3	118.1(2)	C10—N12—C17	117.90(18)
O14—C13—O15	122.9(2)	C13—N12—C17	111.52(18)

O14—C13—N12	128.9(2)	C5—C6—C7	120.8(2)
O15—C13—N12	108.24(19)	C20—C19—C18	120.5(2)
C7—C8—C3	122.7(2)	C25—C24—C1	115.57(18)
C7—C8—O9	124.5(2)	O9—C1—C10	108.26(17)
C3—C8—O9	112.80(18)	O9—C1—C24	108.17(16)
C8—C7—C6	117.2(2)	C10—C1—C24	110.40(18)
O26—C5—C4	123.6(2)	O9—C1—C2	106.49(16)
O26—C5—C6	115.24(19)	C10—C1—C2	114.32(17)
C4—C5—C6	121.1(2)	C24—C1—C2	108.97(18)
C22—C21—C20	120.0(2)	O15—C16—C17	105.89(18)
C8—C3—C4	120.1(2)	N12—C17—C18	113.36(17)
C8—C3—C2	108.89(19)	N12—C17—C16	100.16(17)
C4—C3—C2	131.0(2)	C18—C17—C16	113.32(18)
C23—C18—C19	119.06(19)	C21—C22—C23	120.0(2)
C23—C18—C17	118.74(19)	O11—C10—N12	117.37(19)
C19—C18—C17	122.12(19)	O11—C10—C1	120.7(2)
C19—C20—C21	119.8(2)	N12—C10—C1	121.9(2)

Step 4. (2*S*)-5-[3-(2-Chloro-4-trifluoromethoxy-phenoxy)-propoxy]-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid

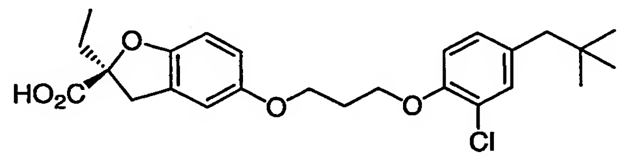
The title compound was prepared following the general procedure described in Example 1, Step 4, employing the chiral phenol prepared in Step 2 and the iodide prepared in Example 3, Step 2.

^{1}H NMR (500MHz, CD_3OD) δ 7.31 (d, J=2.5 Hz, 1H), 7.17 (dd, J_1=8.0, 2.5 Hz, 1H), 7.12 (d, J=8.5 Hz, 1H), 6.78 (br. s, 1H), 6.69 (dd, J=8.0, 2.0 Hz, 1H), 6.66 (d, J=8.5 Hz, 1H), 4.22 (t, J=6.0 Hz, 2H), 4.11 (t, J=6.0 Hz, 2H), 3.47 (d, J=16.0 Hz, 1H), 3.14 (d, J=16.0 Hz, 1H), 2.24-2.19 (quintet, J=6.0 Hz, 2H), 2.03 (dq, J=14.0, 7.5 Hz, 1H), 1.93 (dq, J=14.0, 7.5 Hz, 1H), 0.98 (t, J=7.5 Hz, 3H).

MS (ESI, m/z): 482.3 (M^++Na)

Example 11

(2*S*)-5-{3-[2-Chloro-4-(2,2-dimethyl-propyl)-phenoxy]-propoxy}-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid



Step 1. 2-chloro-1-(3-iodo-propoxy)-4-(2,2-dimethylpropyl)-benzene

The title compound was prepared following the general procedure described in Example 1, Step 3 using the 2-chloro-4-neopentylphenol as the 2,4-disubstituted phenol.

Step 2. (2*S*)-5-{3-[2-Chloro-4-(2,2-dimethyl-propyl)-phenoxy]-propoxy}-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid

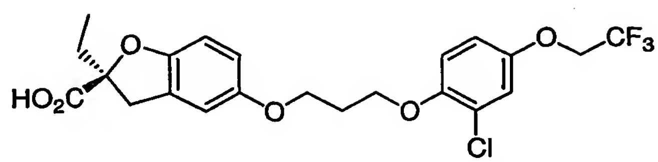
The title compound was prepared following the general procedure described in Example 1, Step 4 employing the chiral phenol prepared in Example 10, Step 2 and the iodide prepared in Step 1.

^{1}H NMR (500MHz, $CDCl_3$) δ 7.11 (d, J=1.5 Hz, 1H), 6.98 (dd, J= 8.0, 1.5 Hz, 1H), 6.95 (d, J= 8.0 Hz, 1H), 6.79 (d, J=2.0 Hz, 1H), 6.70 (dd, J=8.5, 2.0 Hz, 1H), 6.67 (d, J=8.5Hz, 1H), 4.17 (t, J=6.0 Hz, 2H), 4.12 (t, J=6.0 Hz, 2H), 3.48 (d, J=16.5 Hz, 1H), 3.15 (d, J=16.5 Hz, 1H), 2.20 (m, 2H), 2.02 (dq, J=14.5, 7.5 Hz, 1H), 1.93(dq, J=14.5, 7.5 Hz, 1H), 0.99 (t, J=7.5 Hz, 3H), 0.88 (s, 9H).

MS (ESI, m/z): 447.2 (M^++1).

Example 12

(2*S*)-5-{3-[2-Chloro-4-(2,2,2-trifluoro-ethoxy)-phenoxy]-propoxy}-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid



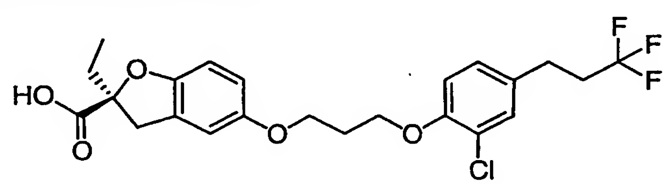
The title compound was prepared following the general procedure described in Example 1, Step 4 employing the chiral phenol prepared in Example 10, Step 2 and the iodide prepared in Example 1, Step 3.

^{1}H NMR (500MHz, CDCl3) δ 7.08 (d, J=2.5 Hz, 1H), 7.02 (d, J= 9.0, 1H), 6.91 (dd, J= 9.0, 2.5 Hz, 1H), 6.79 (d, J=2.0Hz, 1H), 6.70 (dd, J=8.5, 2.0 Hz, 1H), 6.67 (d, J=8.5 Hz, 1H), 4.46 (q, J=8.5 Hz, 2H), 4.16 (t, J=6.0 Hz, 2H), 4.11 (t, J=6.0 Hz, 2H), 3.48 (d, J=16.5 Hz, 1H), 3.16 (d, J=16.5 Hz, 1H), 2.20 (m, 2H), 2.03 (dq, J=14.5, 7.5 Hz, 1H), 1.94(dq, J=14.5, 7.5 Hz, 1H), 0.99 (t, J=7.5 Hz, 3H).

MS (ESI, m/z): 474.1 (M$^+$).

Example 13

(2*S*)-5-{3-[2-Chloro-4-(3,3,3-trifluoro-propyl)-phenoxy]-propoxy}-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid



Step 1. 2-Chloro-4-(3,3,3-trifluoro-propyl)phenol

A solution of 4-benzyloxy-3-chlorobenzaldehyde (0.25 g, 2. 0 mmol), 2,2,2-trifluoroethyltriphenylphosphonium trifluoromethanesulfonate (0.49 g, 1.0 mmol) and CsF (0.76 g, 5.0 mmol) in DMF (10 mL) was stirred at 25 °C for 16 h. The reaction was then diluted with ethyl acetate, washed with water and dried. Removal of the solvent gave a residue which was purified by preparative TLC to give 1-(3-chloro-4-benzyloxyphenyl)-3,3,3-trifluoropropene. This product (65 mg, 0.2 mmol) was dissolved in ethyl acetate (2 mL) and hydrogenated (1 atm) in the presence of 10%

palladium on carbon for 1 hr. Removal of the catalyst and solvent give 2-chloro-4-(3,3,3-trifluoropropyl)phenol as an oil.

Step 2. Preparation 2-chloro-1-(3-iodo-propoxy)-4-(3,3,3-trifluoropropyl)-benzene.

The iodide was prepared following the general procedure described in Example 1, step 3 using the phenol prepared in step 1 as *para*-substituted phenol.

Step 3. (2*S*)-5-{3-[2-Chloro-4-(3,3,3-trifluoro-propyl)-phenoxy]-propoxy}-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid

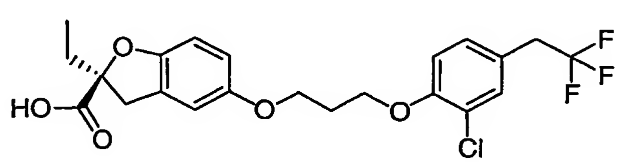
The title compound was prepared following the general procedure described in Example 1, Step 4 employing the chiral phenol in Example 10, Step 2 and the iodide prepared in Step 2.

^{1}H NMR (500MHz, CD_3OD) δ 7.26 (d, J=2.5 Hz, 1H), 7.11 (dd, J=8.5, 2.5 Hz, 1H), 6.70 (d, J=8.5 Hz, 1H), 6.79 (br. s, 1H), 6.71-6.66 (m, 2H), 4.18 (t, J=6.0 Hz, 2H), 4.12 (t, J=6.0 Hz, 2H), 3.47 (d, J=16.0 Hz, 1H), 3.15 (d, J=16.0 Hz, 1H), 2.80-2.77 (m, 2H), 2.47-2.37 (m, 2H), 2.24-2.18 (m, 2H), 2.04 (dq, J=14.0, 7.5Hz, 1H), 1.93 (dq, J=14.0, 7.5Hz, 1H), 0.99 (t, J=7.5 Hz, 3H).

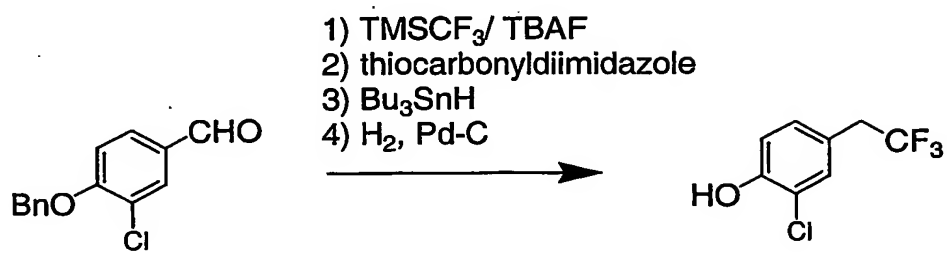
MS (ESI, m/z): 495.1 (M^++Na).

Example 14

(2*S*)-5-{3-[2-Chloro-4-(2,2,2-trifluoro-ethyl)-phenoxy]-propoxy}-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid



Step 1. 2-Chloro-4-(2,2,2-trifluoro-ethyl)phenol



To a solution of 4-benzyloxy-3-chlorobenzaldehyde (4.9 g, 20 mmol) and trimethyl(trifluoromethyl)silane (4.4 mL, 30 mmol) in THF (0.10 L) was added a solution tetrabutylammonium fluoride (1.0 M in THF, 2.0 mL). After the reaction was stirred at 25 °C for 3 h, it was acidified with 2 *N* HCl to pH 2, diluted with ethyl acetate and washed with brine. The organic phase was dried and concentrated and the residue was purified by chramotography on silica gel eluting with 8:2 hexane:ethyl acetate to give 1-(4-benzyloxy-3-chlorophenyl)-2,2,2-trifluoroethanol.

1-(4-Benzyloxy-3-chlorophenyl)-2,2,2-trifluoroethanol (5.1 g, 16.1 mmol) and thiocarbonyldiimidazole (4.3 g, 24.2 mmol) were dissolved in THF (50 mL) and the solution was heated under reflux for 2 hrs. The reaction mixture was diluted with ethyl acetate, washed with brine and dried. Removal of solvent give crude 1-(4-benzyloxy-3-chlorophenyl)-2,2,2-trifluoroethyl *N*-imidazolyl thiocarbonate which is directly used for the next reaction.

1-(4-Benzyloxy-3-chlorophenyl)-2,2,2-trifluoroethyl *N*-imidazolyl thiocarbonate (crude, 7.0 g , *ca* 16.1 mmol), tributyltin hydride (6.9 g, 24.2 mmol) and AIBN (0.53 g, 3.2 mmol) were mixed in toluene and the resulting solution was heated at 85 °C under nitrogen for 3 hrs. The reaction mixture was concentrated and the residue was purified by chromatography on silica gel eluting sequentially with 100% hexane and 10 :1 hexane:ethyl acetate to give 1-benzyloxy-2-chloro-4-(2,2,2-trifluoro-ethyl)benzene.

1-Benzyloxy-2-chloro-4-(2,2,2-trifluoro-ethyl)benzene (4.0 g, 13.0 mmol) was dissolved in dichloromethane (50 mL) and cooled to – 78 °C. A solution of boron tribromide (1.0 M in CH_2Cl_2, 14.3 mL, 14.3 mmol) was added. The reaction mixture was warmed to 0°C, diluted with dichloromethane and washed with brine. After removal of solvent, the residue was chromatographed on silica gel eluting with 9:1 hexane:ethyl acetate to give the title compound.

^{1}H NMR (500MHz, CD_3Cl) δ 7.32 (d, J=2.0 Hz, 1H), 7.22 (dd, J=8.5, 2.0 Hz, 1H), 7.06 (d, J=8.5 Hz, 1H), 4.50 (br.s, 1H), 3.48 (q, J=11.0 Hz, 2H).

Step 2. 2-Chloro-1-(3-iodo-propoxy)-4-(2,2,2-trifluoro-ethyl)benzene.

The title compound was prepared following the general procedure described in Example 1, step 3 using the phenol prepared in step 1 as *para*-substituted phenol.

Step 3. (2*S*)-5-{3-[2-Chloro-4-(2,2,2-trifluoro-ethyl)-phenoxy]-propoxy}-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid

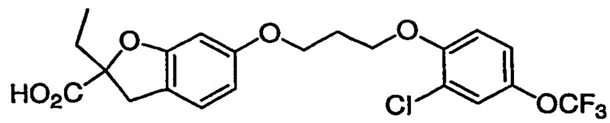
The title compound was prepared following the general procedure described in Example 1, Step 4, employing the chiral phenol prepared in Example 10, Step 2 and the iodide prepared in Step 2.

^{1}H NMR (500MHz, CD_3OD) δ 7.35 (d, J=2.0 Hz, 1H), 7.21 (dd, J_1=8.5, 2.0 Hz, 1H), 7.06 (d, J=8.5 Hz, 1H), 6.80 (d, J=2.0 Hz, 1H), 6.70 (dd, J=8.5, 2.0Hz, 1H), 6.68 (d, J=8.5 Hz, 1H), 4.22 (t, J=6.5 Hz, 2H), 4.14 (t, J=6.5 Hz, 2H), 3.48 (d, J=16.0 Hz, 1H), 3.48 (q, J=11.0 Hz, 2H), 3.16 (d, J=16.0 Hz, 1H), 2.23 (quintet, J=6.5 Hz, 2H), 2.03 (dq, J=14.0, 7.5 Hz, 1H), 1.93 (dq, J=14.0, 7.5 Hz, 1H), 0.99 (t, J=7.5 Hz, 3H).

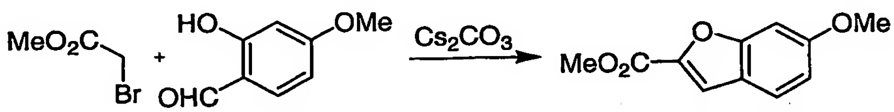
MS (ESI, m/z): 481.0 (M^++Na).

Example 15

6-[3-(2-Chloro-4-trifluoromethoxy-phenoxy)-propoxy]-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid

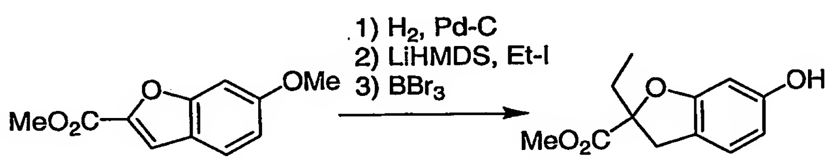


Step 1. Preparation of 6-methoxy-benzofuran-2-carboxylic acid methyl ester.



A mixture of methyl bromoacetate (1.53 g, 10 mmol), 2-hydroxy-4-methoxybenzaldehyde (1.52 g, 10 mmol) and Cs_2CO_3 (6.5 g, 20 mmol) in DMF (100 mL) was stirred vigorously at 50 °C for 3 hrs and then at 150 °C for 5 min. The reaction was cooled, diluted with ethyl acetate and washed with water. The organic phase was dried and concentrated to give essentially pure 6-methoxy-benzofuran-2-carboxylic acid methyl ester as a solid.

Step 2. 2-Ethyl-6-hydroxy-2,3-dihydro-benzofuran-2-carboxylic acid methyl ester.



The title compound was prepared following the procedure described in Example 1, Step 1 employing methyl 6-methoxy-benzofuran-2-carboxylate instead of methyl 5-methoxy-benzofuran-2-carboxylate and ethyl iodide instead of methyl iodide.

^{1}H NMR (500MHz, CDCl3) δ 6.97 (d, J=8.5 Hz, 1H), 6.44 (d, J= 2.5 Hz, 1H), 6.37 (dd, J= 8.5, 2.5 Hz, 1H), 3.81 (s, 3H), 3.49 (d, J=16.0 Hz, 1H), 3.13 (d, J=16.0 Hz, 1H), 2.08 (dq, J=14.5, 7.5 Hz, 1H), 2.01(dq, J=14.5, 7.5 Hz, 1H), 1.00 (t, J=7.5 Hz, 3H).

Step 2. 6-[3-(2-Chloro-4-trifluoromethoxy-phenoxy)-propoxy]-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid

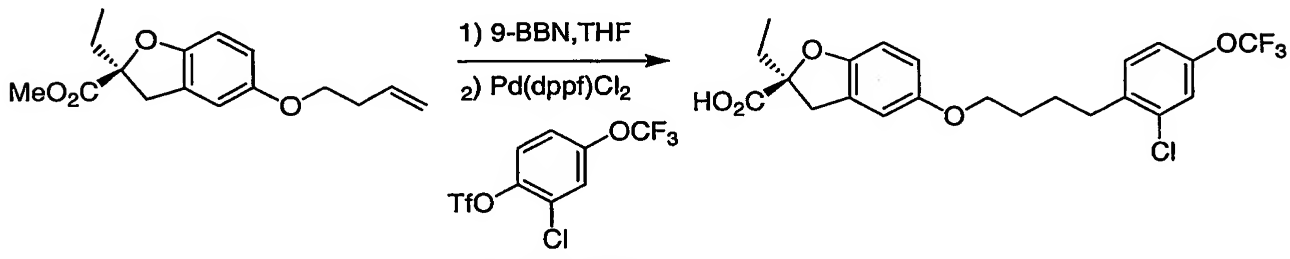
The title compound was prepared following the general procedure described in Example 1, Step 4, employing the phenol prepared in Step 2 and the iodide prepared in Example 3, Step 2.

^{1}H NMR (500MHz, CD_3OD) δ 7.32 (d, J=2.0 Hz, 1H), 7.19 (dd, J=8.5, 2.0 Hz, 1H), 7.13 (d, J=8.5 Hz, 1H), 6.99 (d, J= 9.0 Hz, 1H), 6.41-6.46 (m, 2H), 4.23 (t, J=6.0 Hz, 2H), 4.15 (t, J=6.0 Hz, 2H), 3.42 (d, J=16.5 Hz, 1H), 3.11 (d, J=16.5 Hz, 1H), 2.23 (m, 2H), 2.03 (dq, J=14.5, 7.5 Hz, 1H), 1.94(dq, J=14.5, 7.5 Hz, 1H), 0.99 (t, J=7.5 Hz, 3H).

MS (ESI, m/z): 461.2 (M^++1).

Example 16

(2*S*)- 5-[4-(2-Chloro-4-trifluoromethoxy-phenyl)-butoxy]-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid



Step 1. (2*S*)-5-But-3-enyloxy-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid methyl ester.

A mixture of methyl (2*S*)-2-ethyl-5-hydroxy-2,3-dihydro-benzofuran-2-carboxylate (0.22 g, 1.0 mmol), prepared in Example 10, Step 2, 4-bromo-1-butene (1.35 g, 10 mmol) and Cs_2CO_3 (1.63 g, 5.0 mmol) in DMF (20 mL) was stirred at 50

°C for 16 hrs. The reaction was diluted with ethyl acetate and washed with water. After removal of the solvent, the reisdue was purified by preparative TLC to give 0.14 g (2*S*)-5-But-3-enyloxy-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid methyl ester.

Step 2. Trifluoromethanesulfonic acid 2-chloro-4-trifluoromethoxy-phenyl ester.

To a solution of 2-chloro-4-trifluoromethoxyphenol (0.21 g, 1.0 mmol) and ethyldiisopropylamine (0.27 g, 2.0 mmol) in dichloromethane (10 mL) cooled at -78 °C was added dropwise trifluoromethanesulfonic anhydride (0.31 g, 1.1 mmol). The reaction was warmed to 25 °C and concentrated. The residue was triturate with diethyl ether and filtered through a pad of silica gel. Concentration of the filtrate gave the title compound, which was used directly for the coupling reaction in step 3.

Step 3. (2*S*)-5-[4-(2-Chloro-4-trifluoromethoxy-phenyl)-butoxy]-2-ethyl-2,3-dihydro-benzofuran-2-carboxylic acid

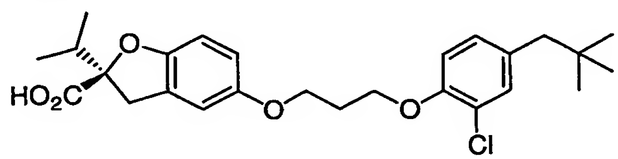
To solution of 5-[(buten-3-yl)oxy]-2-ethyl2,3-dihydro-1-benzofurancarboxylate (0.14 g, 0.50 mmol, prepared in step 1) in THF (5 mL) was added 9-BBN (1.0 M THF, 0.55 mL, 0.55 mmol). After 5 hrs at 25 °C, the solution was added to a mixture of the triflate prepared in step 2 (0.29 g, 1.0 mmol), $Pd(dppf)Cl_2$ (73 mg, 0.1 mmol) and K_2CO_3 (0.21 g, 1.5 mmol) in DMF (5 mL), and the reaction mixture was heated at 60 °C for 6 h. The reaction was diluted with ethyl acetate and washed with water. The organic phase was dried and concentrated. The residue was purified by preparative TLC (8:2 hexane:ethyl acetate) to give methyl 5-{4-[2-chloro-4-(trifluoromethoxy)phenyl]butyl}-2-ethylbenzo-2,3-dihydro-furan-2-carboxylate, which was hydrolyzed with KOH under general conditions described in Example 1, Step 4.

^{1}H NMR (500MHz, CD_3OD) δ 7.40 (d, J=8.5 Hz, 1H), 7.31 (d, J= 1.5 Hz, 1H), 7.18 (dd, J= 8.5, 1.5 Hz, 1H), 6.76 (s, 1H), 6.65-6.69 (m, 2H), 3.92 (t, J=6.0 Hz,2H), 3.48 (d, J= 16.5 Hz, 1H), 3.17 (d, J=16.5, 1H), 2.82 (t, J=6.0 Hz, 1H), 2.03 (dq, J=14.5, 7.5 Hz, 1H), 1.94(dq, J=14.5, 7.5 Hz, 1H), 1.75-1.83 (m, 4H), 0.99 (t, J=7.5 Hz, 3H).

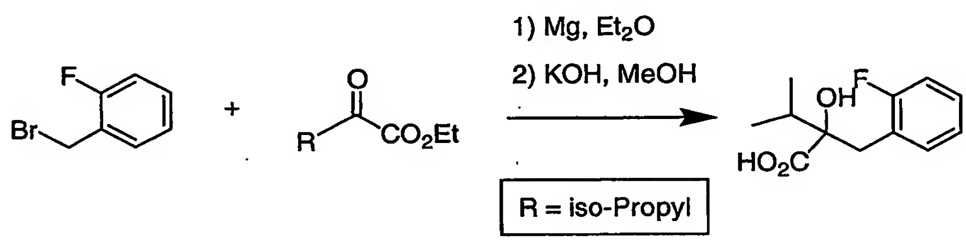
MS (ESI, m/z): 459.2 (M^++1).

Example 17

(2*R*)-5-{3-[2-Chloro-4-(2,2-dimethyl-propyl)-phenoxy]-propoxy}-2-isopropyl-2,3-dihydro-benzofuran-2-carboxylic acid



Step 1. 2-(2-Fluoro-benzyl)-2-hydroxy-3-methyl-butyric acid

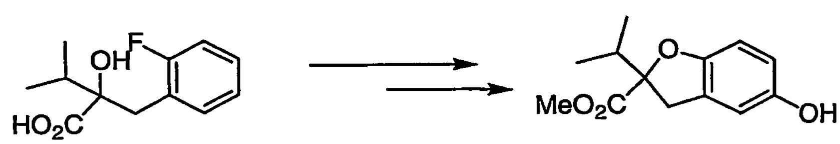


A solution of (*o*-fluorobenzyl)magnesium bromide in diethyl ether (100 mL), prepared from the corresponding *o*-fluorobenzyl bromide (9.45 g, 50.0 mmol) and magnesium turnings (1.32 g, 55.0 mmol), was added to a solution of ethyl 3-methyl-2-oxobutanoate (7.2 g, 50 mmol) in diethyl ether (50 mL) cooled at -78 °C. After 30 min at –78 °C, the reaction mixture was warmed to 0 °C and poured into saturated aqueous NH_4Cl. The organic layer was washed with brine, dried and concentrated. The residue was dissolved in methanol (200 mL) and kept with 2 *N* KOH (75 mL) for 2 hrs. at 50 °C. The reaction mixture was diluted with water and washed with hexane. The aqueous layer was acidified with 2 *N* HCl, saturated with

sodium chloride and extracted with ethyl acetate. Removal of solvents gave the title compound.

^{1}H NMR (500MHz, CDCl3) δ 7.30-7.35 (m, 1H), 7.18-7.23 (m, 1H), 7.06 (t, , J=7.8 Hz, 1H), 7.00 (dd, J= 7.8, 9.0 Hz, 1H), 3.17 (d, J=14.0 Hz, 1H), 3.05 (d, J=14.0 Hz, 1H), 2.18 (m, 1H), 1.1 (t, J=7.5 Hz, 3H), 0.90 (t, J=7.5 Hz, 3H).

Step 2. (±)-5-Hydroxy-2-isopropyl-2,3-dihydro-benzofuran-2-carboxylic acid methyl ester



The title compound was prepared following the procedure described in Example 10, Step 2, employing 2-(2-fluoro-benzyl)-2-hydroxy-3-methyl-butyric acid instead of 2-(2-fluoro-benzyl)-2-hydroxy-butyric acid.

Step 3. (2*R*)-5-Hydroxy-2-isopropyl-2,3-dihydro-benzofuran-2-carboxylic acid methyl ester

A racemic mixture of the intermediate prepared in step 2 was separated by preparative HPLC on a 2.0 × 25 cm Chiracel OD column eluting with 1:9 isopropyl alcohol : heptane with a flow rate of 6.0 ml/min. The fraction corresponding to the second peak was collected and concentrated to give the title compound. The stereochemistry of the title compound at the chiral center was assigned *R* based on the assumption that the elution order of the two enantiomers on the chiral OD column was the same as the elution order of the two enantiomers of the corresponding 2-ethyl-substituted analog described in Example 10, Step 2, where X-ray crystallography was used for the determination of the absolute stereochemistry.

^{1}H NMR (500MHz, CDCl3) δ 6.72 (d, J=8.5 Hz, 1H), 6.67 (d, J=3.0 Hz, 1H), 6.61 (dd, J=8.5, 3.0 Hz, 1H), 4.82 (br. s, 1H), 3.81 (s, 3H), 3.53 (d, J=16.5 Hz, 1H), 3.23 (d, J=16.5 Hz, 1H), 2.33 (m, 1H), 1.02 (d, J=6.5 Hz, 3H), 0.97 (d, J=6.5 Hz, 3H) .

Step 4. (2*R*)-5-{3-[2-Chloro-4-(2,2-dimethyl-propyl)-phenoxy]-propoxy}-2-isopropyl-2,3-dihydro-benzofuran-2-carboxylic acid

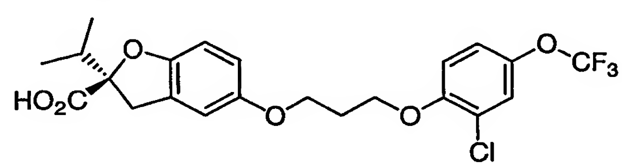
The title compound was prepared following the general procedure described in Example 1, Step 4, employing the chiral phenol prepared in Step 3 and the iodide prepared in Example 11, Step 1.

^{1}H NMR (500MHz, CD_3OD) δ 7.11 (d, J=1.5 Hz, 1H), 6.98 (dd, J= 8.0, 1.5 Hz, 1H), 6.94 (d, J= 8.0 Hz, 1H), 6.77 (d, J=2.0 Hz, 1H), 6.65-6.71 (m, 2H), 4.17 (t, J=6.0 Hz, 2H), 4.11 (t, J=6.0 Hz, 2H), 3.44 (d, J=16.5 Hz, 1H), 3.25 (d, J=16.5 Hz, 1H), 2.40(s, 2H), 2.25 (septet, J= 7.5 Hz, 1H), 2.19 (quintet, J=7.5 Hz, 1H), 1.01 (d, J=7.5 Hz, 3H), 0.94 (d, J=7.5 Hz, 3H), 0.87 (s, 9H).

MS (ESI, m/z): 461.3 (M^+).

Example 18

(2*R*)-5-[3-(2-Chloro-4-trifluoromethoxy-phenoxy)-propoxy]-2-isopropyl-2,3-dihydro-benzofuran-2-carboxylic acid



The title compound was prepared following the general procedure described in Example 1, Step 4, employing the chiral phenol prepared in Example 18, Step 3 and the iodide prepared in Example 3, Step 2.

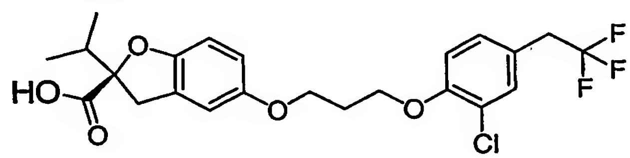
^{1}H NMR (500MHz, CD_3OD) δ 7.33 (d, J=2.0 Hz, 1H), 7.20 (dd, J= 8.0, 2.0 Hz, 1H), 7.15 (d, J= 8.0 Hz, 1H), 6.73 (s, 1H), 6. 62-6.66 (m, 2H), 4.24 (t, J=6.0 Hz, 2H), 4.11

(t, J=6.0 Hz, 2H), 3.44 (d, J=16.5 Hz, 1H), 3.18 (d, J=16.5 Hz, 1H), 2.22 (quintet, J=7.5 Hz, 2H), 1.02(d, J=7.5 Hz, 3H), 0.89 (d, J=7.5 Hz, 3H).

MS (ESI, m/z): 497.1 (M^++Na).

Example 19

(2*R*)-5-{3-[2-Chloro-4-(2,2,2-trifluoro-ethyl)-phenoxy]-propoxy}-2-isopropyl-2,3-dihydro-benzofuran-2-carboxylic acid



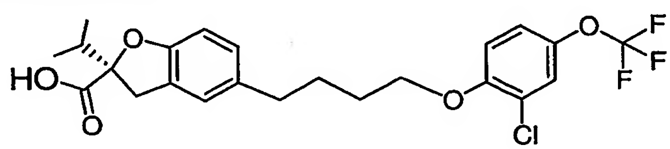
The title compound was prepared following the general procedure described in Example 1, Step 4, employing the chiral phenol prepared in Example 18, Step 3 and the iodide prepared in Example 14, Step 2.

^{1}H NMR (600MHz, CD_3OD) δ 7.32 (d, J=1.8 Hz, 1H), 7.19 (dd, J_1=8.4, 1.8 Hz, 1H), 7.04 (d, J=8.4 Hz, 1H), 6.72 (br. s, 1H), 6.61-6.64 (m, 2H), 4.20 (t, J=6.0 Hz, 2H), 4.09 (t, J=6.0 Hz, 2H), 3.42 (d, J= 16.8 Hz, 1H), 3.39 (q, J= 10.8 Hz, 2H), 3.2 (d, J=16.8 Hz, 1H), 2.24-2.17 (m, 3H), 1.00 (d, J=6.6 Hz, 3H), 0.87 (d, J=7.2 Hz, 3H).

MS (ESI, m/z): 473.3 (M^++1).

Example 20

(2*R*)-5-[4-(2-Chloro-4-trifluoromethoxy-phenoxy)-butyl]-2-isopropyl-2,3-dihydro-benzofuran-2-carboxylic acid



Step 1. 4-[2-Chloro-4-(trifluoromethoxy)phenoxy]-1-butene

The title compound was prepared following the procedure described in Example 16, Step 1, employing 2-chloro-4-(trifluoromethyl)phenol instead of methyl (2*S*)-2-ethyl-5-hydroxy-2,3-dihydro-benzofuran-2-carboxylate.

Step 2. (2*R*)-5-[(Trifluoromethanesulfonyl)oxy]-2-isopropyl-2,3-dihydro-benzofuran-2-carboxylic acid methyl ester.

The title compound was prepared following the precedure described in Example 16, Step 2, employing methyl (2*R*)-5-hydroxy-2-isopropyl-2,3-dihydro-benzofuran-2-carboxylate instead of 2-chloro-4-(trifluoromethoxy)phenol.

Step 3. (2*R*)-5-[4-(2-Chloro-4-trifluoromethoxy-phenoxy)-butyl]-2-isopropyl-2,3-dihydro-benzofuran-2-carboxylic acid

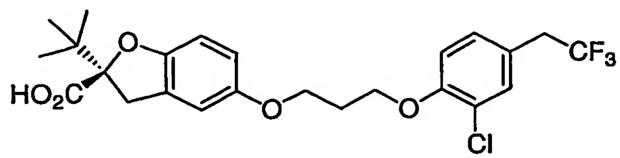
The title compound was prepared following the procedure described in Example 16, Step 3, employing the intermediate prepared in Step 1 instead of 5-[(buten-3-yl)oxy]-2-ethyl2,3-dihydro-1-benzofurancarboxylate and the triflate prepared in Step 2 instead of 2-chloro-4-(trifluoromethoxy)phenyl trifluoromethanesulfonate.

^{1}H NMR (500MHz, CD_3OD) δ 7.33 (d, J=2.5 Hz,1H), 7.18 (dd, J=9.0, 2.5Hz, 1H), 7.08 (d, J=9.0 Hz, 1H), 7.01 (br. s, 1H), 6.95 (d, J=8.0 Hz, 1H), 6.75 (d, J=8.0 Hz, 1H), 4.06 (t, J=6.0 Hz, 2H), 3.46 (d, J=16.5 Hz, 1H), 3.29 (d, J=16.5 Hz, 1H), 2.63 (t, J= 7.0 Hz, 1H), 2.28 (m, 1H), 1.76-1.87 (m, 4H), 1.03 (d, J=6.5 Hz, 3H), 0.96 (d, J=6.5 Hz, 3H).

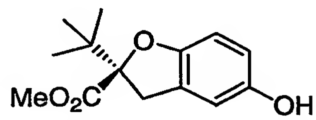
MS (ESI, m/z): 495.0 (M^++Na)

Example 21

(2*R*)- 2-*tert*-Butyl-5-{3-[2-chloro-4-(2,2,2-trifluoro-ethyl)-phenoxy]-propoxy}-2,3-dihydro-benzofuran-2-carboxylic acid



Step 1. Preparation of 2-*tert*-Butyl-5-hydroxy-2,3-dihydro-benzofuran-2-carboxylic acid methyl ester



The title compound was prepared following the procedure described in Example 17, Steps 1, 2 and 3, employing methyl 3,3-dimethyl-2-oxobutanoate instead of methyl 3-methyl-2-oxobutanoate in the first step.

^{1}H NMR (500MHz, $CDCl_3$) δ 6.72 (d, J=8.5 Hz, 1H), 6.67 (d, J=3.0 Hz, 1H), 6.61 (dd, J=8.5, 3.0 Hz, 1H), 4.90 (br. s, 1H), 3.81 (s, 3H), 3.40 (s, 2H), 1.1 (s, 9H).

Step 2. (2*R*)- 2-*tert*-Butyl-5-{3-[2-chloro-4-(2,2,2-trifluoro-ethyl)-phenoxy]-propoxy}-2,3-dihydro-benzofuran-2-carboxylic acid

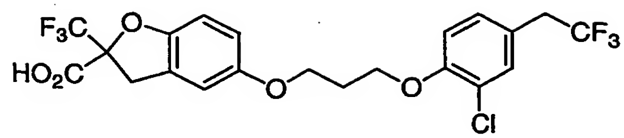
The title compound was prepared following the general procedure described in Example 1, Step 4, employing the chiral phenol prepared in step 1 and the iodide prepared in Example 14, Step 2.

^{1}H NMR (500MHz, CD_3OD) δ 7.33 (s, 1H), 7.20 (d, J= 8.0 Hz, 1H), 7.05 (d, J= 8.0 Hz, 1H), 6.79 (s, 1H), 6. 70 (br. s, 2H), 4.21 (t, J=6.0 Hz, 2H), 4.12 (t, J=6.0 Hz, 2H), 3.40 (q, J=11.0 Hz, 2H), 3.39 (s, 2H), 2.22 (quintet, J=7.5 Hz, 2H), 1.07 (s, 9H).

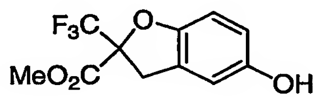
MS (ESI, m/z): 487.9 (M+1).

Example 22

5-{3-[2-Chloro-4-(2,2,2-trifluoro-ethyl)-phenoxy]-propoxy}-2-trifluoromethyl-2,3-dihydro-benzofuran-2-carboxylic acid



Step 1. 5-Hydroxy-2-trifluoromethyl-2,3-dihydro-benzofuran-2-carboxylic acid methyl ester



The title compound was prepared following the procedure described in Example 17, Step 1 and 2, using methyl 3,3,3-trifluoro-2-oxopropanoate instead of methyl 3-methyl-2-oxobutanoate in the first step.

^{1}H NMR (500MHz, CDCl3) δ 6.72 (d, J=8.5 Hz, 1H), 6.67 (d, J=3.0 Hz, 1H), 6.61 (dd, J=8.5, 3.0 Hz, 1H), 5.2 (br. s, 1H), 3.91 (s, 3H), 3.65 (AB system, J=17 Hz, 2H).

Step 2. 5-{3-[2-Chloro-4-(2,2,2-trifluoro-ethyl)-phenoxy]-propoxy}-2-trifluoromethyl-2,3-dihydro-benzofuran-2-carboxylic acid

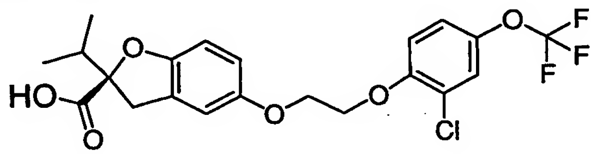
The title compound was prepared following the general procedure described in Example 1, Step 4, employing the phenol prepared in Step 1 and the iodide prepared in Example 14, Step 2.

^{1}H NMR (500MHz, CD_3OD) δ 7.33 (d, J=1.0 Hz, 1H), 7.21 (dd, J= 8.0, 1.0 Hz, 1H), 7.05 (d, J= 8.0 Hz, 1H), 6.87 (s, 1H), 6. 78 (s, 2H), 4.22 (t, J=6.0 Hz, 2H), 4.16 (t, J=6.0 Hz, 2H), 3.65 (AB system, J=17.0 Hz, 2H), 3.40 (q, J = 11.0 Hz, 2H), 2.24 (quintet, J=7.5 Hz, 2H).

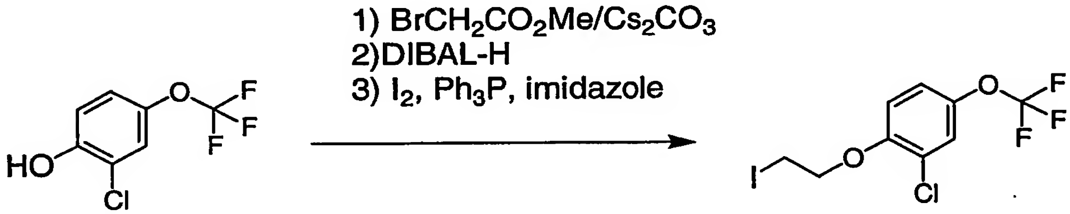
MS (ESI, m/z): 499 (M^++1).

Example 23

(2*R*)-5-[2-(2-Chloro-4-trifluoromethoxy-phenoxy)-ethoxy]-2-isopropyl-2,3-dihydro-benzofuran-2-carboxylic acid



Step 1. 2-Chloro-1-(2-iodo-ethoxy)-4-trifluoromethoxy-benzene



A mixture of 2-chloro-3-(trifluoromethoxy)phenol (2.13 g, 10.0 mmol), methyl bromoacetate (1.8 g, 12 mmol) and Cs_2CO_3 (6.5 g, 20 mmol) in DMF (80 mL) was stirred at 25 °C for 6 hrs. The reaction mixture was diluted with ethyl acetate and washed with water. Removal of solvent give essentially pure methyl 2-[2-chloro-4-(trifluoromethoxy)phenoxy]acetate.

Methyl 2-[2-chloro-4-(trifluoromethoxy)phenoxy]acetate (2.9 g, 10 mmol) was dissolved in dichloromethane (50 mL) and cooled to -78 °C. A solution of diisobutylaluminum hydride in CH_2Cl_2 (1 M, 20 mL) was added and the reaction was warmed to 25 °C over 30 min. The reaction was quenched with methanol (2.0 mL) and poured into 0.5 *N* aqueous HCl. The aqueous phased was extracted with ethyl acetate and the combined organic layers were washed with brine and concetrated. The residue was chromatographed on silica gel eluting with 1:1 hexane:ethyl acetate gave 2-[2-chloro-4-(trifluoromethoxy)phenoxy]ethanol.

2-[2-Chloro-4-(trifluoromethoxy)phenoxy]ethanol was converted to the title compound following the general procedure described in Example 1, Step 3.

Step 2. (2*R*)-5-[2-(2-Chloro-4-trifluoromethoxy-phenoxy)-ethoxy]-2-isopropyl-2,3-dihydro-benzofuran-2-carboxylic acid.

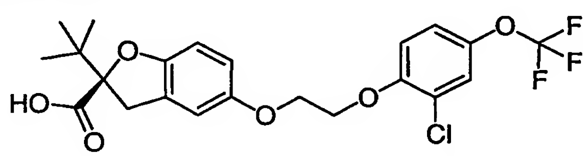
The title compound was prepared following the general procedure described in Example 1, Step 4, employing the phenol prepared in Example 17, Step 3 and the iodide prepared in Step 1.

^{1}H NMR (500MHz, $CDCl_3$) δ 7.30 (d, J=2.5 Hz, 1H), 7.12 (dd, J_1=9.0, 2.5 Hz, 1H), 7.00 (d, J=9.0 Hz, 1H), 6.83 (d, J=2.5 Hz, 1H), 6.81 (d, J=9.0 Hz, 1H), 6.78 (dd, J_1=9.0, 2.5 Hz, 1H), 4.36 (t, J=6.5 Hz, 2H), 4.14 (t, J=6.5 Hz, 2H), 3.56 (d, J=16.5 Hz, 1H), 3.33 (d, J=16.5 Hz, 1H), 2.32 (m, 1H), 1.09 (d, J=7.0 Hz, 3H), 1.02 (d, J=7.0 Hz, 3H).

MS (ESI, m/z): 459.1 (M^+-1)

Example 24

(2*R*)- 2-*tert*-Butyl-5-[2-(2-chloro-4-trifluoromethoxy-phenoxy)-ethoxy]-2,3-dihydro-benzofuran-2-carboxylic acid



The title compound was prepared following the general procedure described in Example 1, Step 4, employing the phenol prepared in Example 21, Step 1 and the iodide prepared in Example 23, Step 1.

^{1}H NMR (600MHz, CD_3OD) δ 7.33 (br.s, 1H), 7.17-7.21 (m, 2H), 6.77 (br. s, 1H), 6.67-6.63 (m, 2H), 4.35-4.32 (m, 2H), 4.26-4.23 (m, 2H), 3.46 (d, J=16.2 Hz, 1H), 3.35 (d, J=16.2 Hz, 1H), 1.04 (s, 9H).

MS (ESI, m/z): 473.1 (M^+-1).